ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 18 November, 1960 Number 11

# NEW FRONTIERS IN ALLERGY

## The Role of Immune Mechanisms in Tissue Transplantation and Resistance to Cancer

GILES A. KOELSCHE, M.D., F.A.C.A.
Rochester, Minnesota

IN RECENT YEARS, the development of new tools, immunologic devices and techniques for allergic investigation has lent impetus to work in this field. Consequently, much basic knowledge relating to allergy and immunology has been acquired, and these disciplines are enjoying respectability and even glamour. Until recently, this latter quality has been largely monopolized by cardiology and endocrinology with their elaborate instruments for clinical investigation.

One frontier in allergy that has led to some fascinating studies, which in turn have produced important immunologic data, is tissue transplantation. Many of the facts acquired from these studies relate to problems of clinical medicine, and the proper use of such information can help physicians solve some of the knotty situations confronting them in their daily practice.

I propose first to review some basic data relating to grafting normal living tissue. I shall then mention some medical situations where this knowledge can be applied.

The transplantation of tissue from one individual to another of the same species usually terminates in ten to fourteen days by sloughing and rejection of the tissue. This is known as the homograft reaction. If the same procedure is repeated one to two weeks later with the same animals, the second graft is rejected more rapidly, usually in five to seven days.

---

Read at the meeting of the Board of Trustees of the Allergy Foundation of America, New York, New York, May 23, 1960.

From the section of medicine, the Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

This is known as the second set reaction and is a type of anamnestic (or "recall") response. In the last several years, these phenomena have attracted greater interest because investigations have indicated that such phenomena represent a specific type of immunologic reaction.

Many studies indicate that the homograft reaction is mediated by the mechanism of delayed hypersensitivity. The graft site becomes infiltrated with lymphoid cells, plasma cells and mononuclear cells some twenty-four to forty-eight hours before rejection takes place. The regional lymph nodes respond to homologous transplantation by lymphoid hyperplasia. Homograft sensitivity is capable of passive transfer by injecting a normal host animal with concentrates of lymphocytes or cells from the regional nodes of the sensitized animal. The normal animal thus passively sensitized reacts to a first homograft with a second set reaction.

Stetson,[14] on the other hand, expressed the opinion, based on his studies, that the white-graft phase of the homograft reaction is dependent on circulating antibodies, since he was able to transfer white-graft immunity passively with the serum from a sensitized animal.

The antigens connected with the homograft reaction are genetically determined by histocompatibility genes.[4] If the recipient animal cannot recognize self-identity markers in the grafted tissue, it promptly begins to build up antibodies against the graft. If the donor and recipient each have the same or almost identical tissue antigens, as would be the case in homozygous twins or highly inbred strains, then the graft is accepted and not rejected. The same obtains when tissue is taken from one site and applied to another site of the same animal. This is known as an autograft.

If the individual receiving the graft does not have in his serum the proteins concerned with antibody activity—a rare condition known as agammaglobulinemia—or if his antibody-producing cells mentioned before —lymphoid, plasma and mononuclear—are destroyed by radiation, nitrogen mustard or cortisone administration or by pretreatment with an antiserum, then the homograft will be accepted. It has also been reported that patients with lymphoma or sarcoidosis will not reject homografts, suggesting that in these naturally occurring conditions the usual immunologic mechanisms are disordered or nonoperative.

The lymphocyte is concerned with recognition of foreign or antigenic material. Lymphocytic nucleoprotein is in equilibrium with that of the various parenchymal cells throughout the body. During fetal life, the lymphocyte is exposed to, and learns to recognize as self, the nucleoproteins (or antigens) of the individual. Thus, homologous, potentially antigenic tissue injected into a fetus will come to be accepted and recognized as self by the lymphocyte. Thereby, a state of immunologic tolerance for the tissue of the donor is produced, and when the inoculated animal reaches adult life, it will accept grafts from the donor of the homologous tissue.[3]

The induction of immunologic tolerance by another ingenious approach

has been reported recently.[13] Pairs of mice, each of which was from a different strain, were joined by parabiosis. When separated some sixty-seven days later, each of a pair showed immunologic tolerance to skin grafts from the other.

Tissue transplantation is employed in the correction of a number of clinical problems. Corneas obtained from Caucasians have been grafted to the eyes of Negroes and other Caucasians and have remained clear. Clouding of the cornea has occurred after grafting from Caucasian to Indian. Subsequent to a slight cold occurring four to six months after a successful transplant, some individuals have experienced cloudiness of the cornea.[7] Some immunologic basis for these observations, though as yet unestablished, seems likely.

It is well known that only autografts will be accepted by human beings for skin grafting following burns or as part of a plastic procedure. However, in the case of identical twins, because the cells of either contain the same self markers, each will accept and retain grafts from the other. A number of instances of successful transplantation of a kidney from one such twin to the other have been reported.[11] In one case, transfer of a kidney from one twin (probably fraternal) to the other was preceded by irradiation of the recipient, temporarily suppressing his immune mechanisms. At last report, the kidney was accepted. Otherwise, homologous transplants of kidneys have been uniformly rejected in man and laboratory animals.

All transplants of bone, whether homografts or autografts, are thought to die initially and then to be revascularized and replaced. It has been observed that these processes take place more rapidly in autografts than in homografts.[9] In the initial phases of vascular surgery, perforce only homografts were used. A number of these would undergo aneurysmal degeneration. Prosthetic devices, rather than arterial homografts, are now used to replace diseased arteries.[8] Proof that hypersensitivity factors are involved in the fate of osseous and vascular homografts has not been obtained.

Let us summarize this area of tissue transplantation. One might observe that if techniques can be discovered which will render human beings immunologically tolerant one to another, it may become possible to transfer successfully various organs or tissues from any individual to another.

Another frontier in allergy concerns immunologic aspects of cancer resistance. This theme has been studied extensively in laboratory animals by means of tumor grafting, which is simply a special part of the general technique of tissue transplantation. Commenting on this means of investigation, Medewar,[10] who is one of its pioneers, observed, "Nearly everyone who supposed he was using transplantation to study tumors was in fact using tumors to study transplantation, not always to good effect."

Cancer tissue exhibits biologic features in regard to homologous transplantation that are similar in type to those of normal tissue. Homografts

of malignant tumors are rejected and undergo second set reactions. They are accepted under normal conditions only by members genetically identical to, or highly inbred with, the strain from which the cancerous animal has come.

Lymphoid cells carry a moiety that has to do with immunity to homologous malignant or normal tissue. Destruction of lymphocytes of an animal afflicted with cancer has led to abrogation of host defenses and stimulation of tumor growth. The administration of lymphocytolytic agents like cortisone, nitrogen mustard or irradiation forestalls the usually expected rejection of a tumor homograft and enables the animal to accept it.

The fact that the serum gamma globulins are increased in moderately advanced malignant disease suggests an immune mechanism in resistance to cancer. Their tendency to decrease as the disease progresses to the preterminal stage suggests a breakdown of the mechanism. Increase in the blood levels of the alpha globulins (or mucoproteins) often is a forerunner of subsequent increased growth of human cancer. Patients with far-advanced malignant disease have decreased blood levels of properdin, a protein having to do with immune reaction. They also show impaired ability to reject tumor homografts.[3]

A number of reported studies suggest that antigenic material present in tumors differs somewhat from that obtained from normal tissue. Gel diffusion-precipitin methods have disclosed in the plasma of patients with carcinoma of the lung an anomalous component that cannot be detected in the plasma of normal individuals.[1] Pooled human carcinomatous tissue has been found to exhibit antigenicity that is different from that shown by normal cells of man.[2] The presence of specific antigens, which are absent in tissues of corresponding healthy organs, has been reported by another group of workers in human cancers of the esophagus, stomach, pancreas, uterus, ovary and male mammary gland. The specific antibodies for these antigens were demonstrated by passive anaphylaxis.[6]

When a preparation of ribonucleic acid extracted from human leukemic blood and solid malignant tumors was injected into mice just before or shortly after birth, 70 per cent of them developed leukemia or malignant tumors. The time elapsing between injection and the appearance of these was 10 to 90 days in the prenatally-treated and three to seven months in the neonatally treated mice. If antisera, prepared in rabbits with the extract of ribonucleic acid, was injected into the mice before they were inoculated with the extract, it prevented the appearance of the tumors.[5]

Cytotoxic antibodies prepared against some transplantable tumors have provided effective passive immunity to subsequent challenge of the animal with tumor cells. Investigators are attempting to enhance the resistance of patients to their malignant disease by the use of autovaccines made from the tumors. The chance of developing a tumor antiserum effective for complete eradication of established solid tumors seems remote.[12]

Factors of host resistance are associated closely with the inception and course of human malignant disease. The spontaneous regression of established tumors, the prolonged survival of some patients after incomplete removal of their cancers, and finally, the sudden appearance of widespread metastases many years after successful treatment of the primary lesion—all indicate strong power of restraint by the patient.[12]

When cells of the body undergo cancerous change, there is an associated variable degree of alteration in their antigenicity. This may involve partial deletion of normal identity markers or creation of a new antigen such as results from entrance of a virus into the cell.[12]

It has been theorized that tumor cells originate in the body by mutation but that those differing most histologically from the host's tissues are contained and destroyed by the immunologic defense mechanisms of the body. Only those tumor cells very similar to the host's cells would have a chance to develop into a tumor because the immune response of the host against such cells would be very weak. This in turn would be true because their self-identity markers would be so similar to the host's that they would not be recognized as foreign and thus would not be antigenic.

Mutation is thought to result from injury to the genetic apparatus of the cell. This insult may be caused by chemical agents, x-rays and even viruses. Mutations caused by the latter add foreign genetic material to the cell. Understanding of cancer immunity may depend on separating and identifying the genetic material, or even the nucleic acid fragments and elucidating the mechanism of action of this material, or these fragments.

Experimentally induced immunologic tolerance will permit malignant cells to grow in animals who otherwise would react to the cells with a homograft rejection. The reason that malignant disease seems to occur in several members of the same family may be because the offspring inherit certain parental malignancy genes. These genes render the offspring immunologically tolerant to malignant cells, so that the cells are not subject to the homograft rejection reaction (or containment and destruction).

In conclusion, experimental evidence suggests that immunologic mechanisms are involved in malignant processes, and one may reasonably hope that in the near future these may be brought to bear more effectively in the treatment of cancer. New frontiers in allergy and associated disciplines have great potential for increasing our basic knowledge in these fields, for elucidating the nature of many perplexing diseases, and for giving direction to their proper management.

## REFERENCES

1. Bernfield, Peter, and Miller, Elizabeth: An anomalous plasma protein in patients with carcinoma of the lung. Proc. Am. A. Cancer Res., 3:95 (Mar.) 1960.
2. Bjorklund, Bertil, and Bjorklund, Viveka: A characteristic antigenic property of human carcinomas. Proc. Am. A. Cancer Res., 3:96 (Mar.) 1960.
3. Black, M. M., and Speer, F. D.: Collective review: Immunology of cancer. Internat. Abstr. Surg., 109:105 (Aug.) 1959.

4. Brent, Leslie: Transplantation immunity and hypersensitivity. *In* Shaffer, J. H., LoGrippo, G. A., and Chase, M. W.: Mechanisms of Hypersensitivity. Pp. 555-568. Boston: Little, Brown and Company, 1959.
5. De Carvalho, S.: Leukemogenic and cancerigenic activity of human leukemic and tumoral RNA in mice. Proc. Am. A. Cancer Res., 3:104 (Mar.) 1960.
6. Gorodilova, V. V., and Shershul'skaia, L. V.: Specific antigens of malignant tumours in man. *In* Vygodchikov, G. V.: Pathogenesis and Immunology of Tumours. (Translated by R. Crawford). Pp. 101-112. New York: Pergamon Press, 1959.
7. Henderson, J. W.: Personal communication to the author.
8. Ivins, J. C.: Personal communication to the author.
9. Lipscomb, P. R.: Personal communication to the author.
10. Medewar, P. B.: Quoted by Black and Speer.[3]
11. Merrill, J. P.: The transplantation of the kidney. Scient. Am., 201:57 (Oct.) 1959.
12. Moore, G. E., and Grace, J. T.: Cancer immunity. Surg., Gynec. & Obst., 110:234 (Feb.) 1960.
13. Shapiro, Fred, Martinez, Carlos, and Good, R. A.: Duration of inter-strain parabiosis on development of tolerance to skin homografts in mice. Proc. Am. A. Cancer Res., 3:150 (Mar.) 1960.
14. Stetson, C. A., Jr.: The role of antibody in the rejection of homografts. *In* Shaffer, J. H., LoGrippo, G. A., and Chase, M. W.: Mechanisms of Hypersensitivity. Pp. 569-573. Boston: Little, Brown and Company, 1959.

*The Mayo Clinic and Mayo Foundation*

---

## FOOD TOXICOLOGY

Since we fear cancer and do not know its cause, when we are told that this or that substance will produce cancer in animals, our natural reaction is to say, "Let's not have any of that in our food." However, the answer is not as simple as that. Some basic nutrients have been shown to produce cancer in animals, for example the injection of a 20 per cent to 25 per cent solution of glucose or of a 5 per cent to 25 per cent solution of ordinary salt. Yet glucose is one of the fundamental nutrients of the body, and salt is a substance without which we cannot survive.

Furthermore, cancer has been produced in experimental animals just by anoxia and also by a diet deficient in choline. In other words, an absence of something also may be carcinogenic.

Obviously, something is wrong with the theory that everything that produces cancer in animals must be banned from our food supply. When we know the cause of cancer we shall be able to make an intelligent evaluation of the presently confusing data on carcinogens. Let us in the meantime try to calm the public hysteria and try to take the pressure off of our governmental officials which may lead to hasty regulations that will look as ridiculous in the future as some of our past efforts to control pestilence look to us today.—W. H. Sebrell, Jr., Institute of Nutrition Sciences, Columbia University School of Public Health and Administrative Medicine, New York, New York; from "Some Problems in Food Toxicology," Fed. Proc., 19:31 (Sept.) 1960.

# STUDIES OF CHLORDIAZEPOXIDE IN VARIOUS ALLERGIC DISEASES

JOHN P. McGOVERN, M.D., F.A.C.A., KEMAL OZKARAGOZ, M.D., GILBERT BARKIN, M.D., THEODORE HAYWOOD, M.D., THOMAS McELHENNEY, M.D., and ALBERT E. HENSEL, JR., M.D.

Houston, Texas

A "HOLISTIC" approach to the therapy of allergic diseases should include not only the use of environmental control measures, specific medication, and injection therapy for hyposensitization, but should also attempt to manage co-existing emotional factors in allergic patients. Intrinsic as well as environmental emotional factors will tend to lower a patient's threshold and help precipitate or exacerbate allergic symptoms.[1]

Since there is tremendous variability among allergic patients, not only in reference to type of disease, but also to frequency, severity and duration of symptoms, evaluation of the effects of psychotherapeutic agents is most difficult. Frequently, we have found it advantageous to give parents, as well as their allergic children, tranquilizing drugs during periods of stress. These drugs tend to diminish anxiety and relieve tensions which aggravate or precipitate the allergic diathesis. The interaction of emotional and environmental factors or obvious manifestations of allergic disease need not be discussed, for there is considerable and readily available literature on the subject.[1-4] For many years, various barbiturate derivatives have been used as an aid in maintaining emotional equilibrium. At present, however, tranquilizing agents are substituted frequently for barbiturates.

Recently a unique psychotherapeutic drug, chlordiazepoxide, was reported to have a calming effect as well as muscle-relaxant qualities in experimental animals.[5] It was decided to study the effects of this drug as an adjunct in the management of patients with allergic diseases and in whom distinct emotional factors co-existed.

Chlordiazepoxide (Librium®)* is chemically unrelated to any of the common "tranquilizing" agents presently in use (Fig. 1). It has been shown to control common emotional disturbances, such as anxiety and tension states, apparently without the dulling of mental acuity or effecting change in personality when given in proper dosage.[6-11] In some patients the drug has been noted to exert a profound antidepressant effect.[8-10]

Although the mode of action of chlordiazepoxide has not been clearly delineated,[5,12] its action seems to be different from that of other psychotherapeutic agents. It has been shown to have a marked appetite-stimu-

From the Departments of Pediatrics and Microbiology, Baylor University College of Medicine and the Allergy Clinic, Junior League Diagnostic Clinic of Texas Children's Hospital, Houston, Texas.

*Obtained from Hoffmann-LaRoche, Inc., Nutley, New Jersey.

lating effect in both experimental animals and in human subjects.[5,13,14] In addition, it appears to have some antipruritic action.[14]

The purpose of this study was to evaluate by double-blind method the effectiveness of chlordiazepoxide as an adjunctive agent in the management

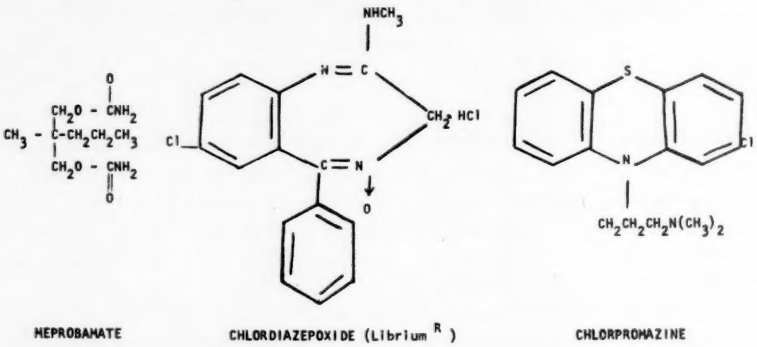


Fig. 1. Difference in basic structural formulae between chlordiazepoxide and two common tranquilizing agents.

of patients manifesting various allergic diatheses. Attempts were made to ascertain any effect on the basic allergic state as well as on emotional status, particularly in allergic children. Also, we wished to determine an adequate, safe dosage schedule for allergic children as well as adults.

## MATERIALS AND METHODS

Patients used in the double-blind study were new patients, ranging in age from two to fourteen years and currently under treatment in the Junior League Allergy Clinic of the Texas Children's Hospital, Houston, Texas. These patients were selected because each had significant emotional overlay which appeared to influence adversely the course and management of the allergic disease. Double-blind control of this drug was outlined by our statistician.** Later, an uncontrolled clinical evaluation was carried out in a group of private patients, both adults and children, in our private allergy clinic.

Dosage schedules were calculated on the basis of square meter of body surface per twenty-four hours, and these amounts were individualized as much as possible.[15] Children in the double-blind study were separated by diagnosis into five groups: (1) those with perennial allergic rhinitis (P.A.R.); (2) asthma; (3) P.A.R. and asthma; (4) eczema; and (5) P.A.R., asthma and eczema, as shown in Table I. There were two additional diagnostic categories—namely, hives and angioedema and the tension-fatigue syndrome—in the nondouble-blind clinical evaluation, as seen in Table II.

**R. A. Seibert, Ph.D., Baylor University College of Medicine, Houston, Texas.

TABLE I. DOSAGE, RESULTS, AND SIDE EFFECTS OF CHLORDIAZEPOXIDE
(50 treated children, double-blind study)

| Study Groups | Number of Patients | Age Range In Years | Severity of Symptoms | | | Range of Daily Dose/M² Surface Area (mg.) | Results | | | | Side Reactions | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mild | Med. | Sev. | | Ex. | G. | F. | P. | Mild | Med. | Sev. |
| I. (P.A.R.) | 6 | 3½-14 | 1 | 3 | 2 | 18-33 | 1 | 4 | 1 | | | 1 | |
| II. (Asthma) | 1 | 11 | | 1 | | 30 | | 1 | | | | | |
| III. (P.A.R. and asthma) | 34 | 2½-13 | 6 | 20 | 8 | 13-34 | 14 | 13 | 4 | 3 | 3 | 1 | |
| IV. (Eczema) | 2 | 2-9 | | 1 | 1 | 22-27 | | 2 | | | | | |
| V. (P.A.R., asthma, and eczema) | 7 | 2-10 | | 1 | 6 | 14-30 | 3 | 2 | | 2 | | | |

Objective and deductive evaluations as to effectiveness or lack of effectiveness by certain criteria were made independently on each patient by each of the individual investigators. Rough estimates of the emotional status of each patient as well as the family unit were made by us in each case before therapy was started. These were on the basis of: (1) statements from child or parent, or both, as to feeling relief of allergic symptoms, increased general feeling of well-being, and relief of tension; (2) comparisons of illness prior to and after beginning chlordiazepoxide or placebo; and (3) impression of teachers of school children before, during and after treatment. The method used can be seen in a sample report shown in Figure 2. Results were evaluated as excellent (very mild or no symptoms); good (moderate control of symptoms); fair (slight but definite improvement); and poor (symptoms remained the same or became more severe).

Patients in the double-blind study were treated with either coded chlordiazepoxide or coded placebo for a period of at least two weeks as determined by an acceptable system of double-blind randomization. Following this treatment period, a known placebo was given for one week in order to allow time for "washout" of any cumulative amounts of chlordiazepoxide. A two-week course of treatment with either the coded preparation of chlordiazepoxide (Librium®) or coded placebo, the one

TABLE II. DOSAGE, RESULTS, AND SIDE EFFECTS OF CHLORDIAZEPOXIDE
(114 patients, clinical evaluation only)

| Study Groups | Number of Patients | Age Range in Years | Severity of Symptoms | | | Range of Daily Dose/M² Surface Area (mg.) | Results | | | | Side Reactions | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mild | Med. | Sev. | | Ex. | G. | F. | P. | Mild | Med. | Sev. |
| I. (P.A.R.) | 34 | 6-83 | 3 | 24 | 7 | 16-56 | 7 | 19 | 4 | 4 | 3 | 3 | 1 |
| II. (Asthma) | 15 | 5-63 | 3 | 8 | 4 | 13-42 | 2 | 4 | 7 | 2 | 2 | 1 | 1 |
| III. (P.A.R. and asthma) | 34 | 3-65 | 3 | 23 | 8 | 6-76 | 8 | 10 | 10 | 6 | 1 | 1 | |
| IV. (Eczema) | 15 | 6-55 | 3 | 7 | 5 | 8-37 | 5 | 9 | 1 | | 2 | | |
| V. (P.A.R., asthma and eczema) | 3 | 6½-47 | | 2 | 1 | 17-40 | 2 | 1 | | | | | |
| VI. (Hives and angioedema) | 4 | 31-39 | | 3 | 1 | 20-40 | 1 | 3 | | | 1 | 1 | |
| VII. (Tension-fatigue) | 9 | 34-40 | | 7 | 2 | 33-40 | 3 | 3 | 3 | | | 1 | |

not used initially, was then started. In the private clinic group, known chlordiazepoxide was given for periods of from 3 to 105 days.

Complete physical examinations were done on all patients. One patient had an asymptomatic congenital heart disease; another was under treatment for grand mal seizures; and two patients in the double-blind group had associated urticaria with P.A.R.

Routine laboratory studies on all patients consisted of complete blood counts, urinalyses and nasal smears. Complete allergic survey, including skin testing, was carried out on each patient. Serum electrolyte, hemogram, transaminase, thymolturbidity and cephalin flocculation determinations were done where indicated.

*Results of Double-Blind Study in Fifty Patients from the J. L. Clinic.*—There were twenty-seven males and twenty-three females ranging in age from two to fourteen years. Dosage of the active drug for twenty-four hours varied from 13 to 34 mg per square meter of body surface area. As can be seen in Table I, this drug gave excellent results in eighteen (36 per cent), good results in twenty-two (44 per cent), fair results in five (10 per cent) and poor results in five (10 per cent) of the patients studied. Poor results were observed in two types of patients: (1) those with severe eczema, and (2) those with deep-seated emotional disturbances which required more than symptomatic treatment. In those cases of eczema with poor results, patients did have moderate relief of itching. The two patients who had urticaria with P.A.R. had no itching while on chlordiazepoxide.

Increase in appetite and weight during the period of active drug therapy was observed in many patients. Three school children showed a definite increased attention span and greater diligence while taking chlordiazepoxide than they had indicated before or after the course of therapy. It was our impression that about 15 mg per square meter per twenty-four hours was a most effective dose without side effects. Side effects were minor, consisting of dizziness, drowsiness and occasionally hyperactivity. These changes appeared between one to six days after the initiation of drug therapy. Three children became pugnacious and quite hyperactive when given twice the usual dose of chlordiazepoxide used in the study. These children then became docile, easily managed, or acted as usual when placed on 13 to 21 mg of chlordiazepoxide per square meter body surface per day. This may be a paradoxical reaction of stimulation rather than calming due possibly to the drug's "psychoenergizing" effect, or a release from inhibitions, or both.[6,15] One child showed ataxia with dosage schedule of 40 mg per square meter body surface area in twenty-four hours. This side effect appeared on the fourth day of therapy and disappeared on the seventh day while the patient was still on the same dose. There was no evidence of habituation, bone marrow depression, extrapyramidal effects, damage to vital organs or photosensitivity. Another patient showed drowsiness on a low-dosage level of the active drug, but also showed similar symptomatology when given the placebo.

PHYSICIAN'S LIBRIUM REPORT FORM (McGovern)

Name John Doe Age 9 yrs. Sex M Marital Status S

Occupation of Parent (or Patient) Post Office Employee School Grade 4th

Diagnoses P.A.R. and Asthma

| Rx Period | Dosage Form | Code Number (Circle One) | Times Daily | Total Daily Dose | Mgm per Sq.M/24h. | Dates of Treatment Period |
|---|---|---|---|---|---|---|
| 1 | 2 mgm | 1 or 2; A or P | | | | to |
| 2 | 2 mgm | 1 or 2; A or P | | | | to |
| 3 | 2 mgm | 1 or 2; A or P | | | | to |
| 1 | 5 mgm | (3) or 4; A or P | 3 | 15 | 13 | March 17, 1960 to April 1, 1960 |
| 2 | 5 mgm | 3 or 4; A or (P) | 3 | 15 | 13 | April 1, 1960 to April 8, 1960 |
| 3 | 5 mgm | 3 or (4); A or P | 3 | 15 | 13 | April 8, 1960 to April 22, 1960 |
| 1 | 10 mgm | 5 or 6; A or P | | | | to |
| 2 | 10 mgm | 5 or 6; A or P | | | | to |
| 3 | 10 mgm | 5 or 6; A or P | | | | to |

INSTRUCTIONS: Give by random proper code # preparation for 2 weeks (Period 1), "P" preparation for one week (Period 2), then other code # preparation of same dosage group for 2 weeks (Period 3).

EVALUATION

| Period | Parent or Patient All. | Anx | Gen. | Wt. | Freq. Att. | Sev. Att. | School Attd. | Atten. Span | Obj. Anx. | Off. Calls | Pho. Calls | Itch | Obj. All. | Side Effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pre-Rx | 4 | 4 | 2 | 69 | 3 | 3 | 1 | 2 | 4 | 1 | 1 | 4 | 4 | 1 |
| Per. 1 | 4 | 4 | 2 | 69 1/4 | 3 | 3 | 1 | 2 | 4 | 1 | 1 | 4 | 4 | 1 |
| Per. 2 | 4 | 3 | 2 | 69 | 3 | 2 | 1 | 2 | 4 | 1 | 1 | 4 | 4 | 1 |
| Per. 3 | 2 | 1 | 1 | 72 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 1 |

All.=Allergy; Anx.=Anxiety & Tension; Gen.=General Well Being, Appetite, Energy; Wt.=Weight: Freq. Att.=Frequency of Attacks; Sev.Att.=Severity of Attacks: Obj.Anx.=Objective Evaluation of Anxiety; Obj.All.=Objective Evaluation of Allergy in General. GRADE RESPONSES: 1=Excellent (Mild or None); 2=Good (Moderate); 3=Fair (Moderately Severe): 4=Poor (Severe)

LIST SIDE EFFECTS HERE None

| Period | Overall Evaluation | Date | Signature | Comments |
|---|---|---|---|---|
| Pre-Rx | 3 | 3/17/60 | | Cooperative reliable parents. |
| Per. 1 | 3 | 4/1/60 | | No appreciable change. |
| Per. 2 | 3 | 4/8/60 | | May be less tense. Allergy the same. |
| Per. 3 | 1+ | 4/22/60 | | Relaxed. Sleeps and eats well. Very little asthma or nasal itching. |

Comments by Date: 4/22/60 Tried him on 30 mg/day of #4. Became as pugnacious as a rattlesnake. Hyperactive. Very tense. Restless.

Code #(3) was the placebo
Code #(4) was chlordiazopoxide (Librium$^{R}$)

Fig. 2.

The drug appeared to be effective in forty instances and not in ten, while the placebo was effective in four and ineffective in forty-six cases. Analysis of the data revealed a *chi* square of 24.58 with a $p$ value of less than 0.001.

*Results of Studies of Patients from Private Allergy Clinic.*—Having determined apparent effectiveness of chlordiazepoxide by a carefully controlled double-blind study, it was decided to extend these observations to 114 similarly selected allergic patients of varying ages from our private allergy clinic. Identical procedure and dosage schedules as those used in the double-blind study were followed, but without placebo control.

There were thirty-eight male and nineteen female children ranging in age from three to fourteen years; sixteen male and forty-one female adults, whose ages were from 16 to 83 years. In the adult group, dosage of the active drug varied from 8 to 56 mg per square meter of body surface area per twenty-four hours. As seen in Table II, by the criteria previously described, this drug gave excellent results in twenty-eight (24 per cent), good results in forty-nine (44 per cent), fair results in twenty-five (22 per cent) and poor results in twelve (10 per cent).

Three patients who had incidental "tension-fatigue" headaches were relieved during the course of therapy, while two patients with migraine headaches were not relieved. Itching of urticaria and of eczema in children was generally diminished, whereas itching in older patients with eczema was unchanged. Marked dermographia in one patient was not affected by chlordiazepoxide. One child with P.A.R. who had associated trichotillomania ceased pulling his hair while receiving the drug.

## DISCUSSION

We realize that clinical studies of drugs of this nature are difficult to control and evaluate, even by the use of double-blind techniques. Nevertheless, our data would strongly suggest the usefulness of this drug as an adjunctive tool in controlling the emotional milieu of allergic patients. Ninety per cent of the patients studied showed some definite improvement by the criteria used. Response to chlordiazepoxide was rapid and in some instances seemed to be of major significance in the control of allergic symptoms. Significant side effects were dose-related, and, in most instances, were controlled by dose reduction. In a few cases it was necessary to cease drug therapy, mainly in geriatric patients, who seemed intolerant even to small doses of the drug. No aggravation of symptoms was noted in the patients with convulsive disorders.[12]

It appeared that the incidence and degree of relief of symptoms closely paralleled improvement in feelings of general well-being, tension, or fatigue. The drug seems to have two actions when given in suitable doses: (1) sedative effect and (2) "antianxiety" effect.[7,12] Most patients showed improvement of sleep habits, which were most marked in the eczema group; this improvement was very likely due to the antipruritic effect and perhaps some resultant "blocking" of tension-fatigue. Hyperhydrosis in one child improved while he was on the active drug. Weight gains of 1 to 7 pounds paralleled stimulation of appetite during two-week periods of therapy. An insatiable two-and-one-half-year-old boy began to raid the neighbor's icebox for the first time.

## SUMMARY AND CONCLUSIONS

1. In a double-blind study, chlordiazepoxide, a new psychotherapeutic agent not related chemically to others currently in use, was found to be effective in reducing emotional patterns and allergic symptoms in forty-five

of fifty allergic children. The usual minimal effective dose was 15 mg per square meter of body surface area per twenty-four hours.

2. The drug also appeared to be effective in 102 of 114 private clinic patients, three to eighty-three years of age.

3. Side effects were ataxia, dizziness, drowsiness and occasionally hyperactivity, easily reversed by dose reduction.

4. Stimulation of appetite with corresponding weight gain was noted in many patients.

5. An antipruritic effect was noted in urticaria, but to a lesser degree in eczema.

6. This drug is not considered a substitute for total antiallergic therapy; its chief value seems to be in reducing emotional quantums which have a profound effect on allergic symptoms.

ACKNOWLEDGMENT

We are greatly indebted to R. A. Seibert, Ph.D., who outlined the double-blind controls. We also wish to thank Marta Courtney, B.S., MT (A.S.C.P.); Barbara Zumwalt; Patsy White, R.N.; Joy Fisk, R.N.; Mary Ann Day, R.N., and Paige Hight for their highly valued technical assistance.

REFERENCES

1. McGovern, John P.: Management of allergy in childhood. Texas J. Med., 54:290, 1958.
2. Bakwin, H. and Bakwin, R. M.: Clinical Management of Behavior Disorders. Philadelphia: Saunders, 1953.
3. Bakwin, Ruth Morris: Essentials of psychosomatics in allergic children. Pediat. Clin. North America, 1:921, 1954.
4. Burgin, Leo B.: Emotion as an "allergen." Pediat. Clin. North America, 6:657, 1959.
5. Randall, Lowell O.: Pharmacology of methaminodiazepoxide. Dis. Nerv. System, 21: (Suppl.) 3, 1960.
6. Kinross-Wright, John, Cohen, Irvin M. and Knight, James A.: The management of neurotic and psychotic states with Ro 5-0690 (Librium). Nerv. Systems, 21: (Suppl.) 3, 23, 1960.
7. Tobin, Joseph M., Bird, Ivan F. and Boyle, Daniel E.: Preliminary evaluation of Librium (Ro 5-0690) in the treatment of anxiety reactions. Dis. Nerv. System, 21: (Suppl.)3, 11, 1960.
8. Farb, Harry H.: Experience with Librium in clinical psychiatry. Dis. Nerv. System, 21: (Suppl.) 3, 27, 1960.
9. Constant, George A.: Preliminary report on the use of a new agent in depression and tension states. Dis. Nerv. System, 21: (Suppl.) 3, 37, 1960.
10. Thomas, Lawrence J.: Preliminary observation on the use of Librium (Ro 5-0690) in internal medicine. Dis. Nerv. System, 21: (Suppl.) 3, 41, 1960.
11. Tickten, Howard E. and Schultz, John D.: Librium, a new quieting drug for hyperactive alcoholic and psychotic patients (preliminary study). Dis. Nerv. System, 21: (Suppl.) 3, 49, 1960.
12. Kaim, Samuel C. and Rosenstein, Ira N.: Anticonvulsant properties of a new psychotherapeutic drug. Dis. Nerv. System, 21: (Suppl.) 3, 46, 1960.
13. Breitner, Carl: Drug therapy in obsessional states and other psychiatric problems. Dis. Nerv. System, 21: (Suppl.) 3, 31, 1960.
14. Robinson, Raymond C. V.: Adjunctive therapy of dermatoses with Librium. Dis. Nerv. System, 21: (Suppl.) 3, 43, 1960.
15. Cohen, Irvin M.: Discussion of papers of Drs. Randall, Tobin, Bowes, Kinross-Wright, *et al.*, Farb and Breitner. Dis. Nerv. System, 21: (Suppl.) 3, 35, 1960.
16. Rosenstein, Ira N.: A new psychosedative (Librium) as an anti-convulsant in grand mal type convulsive seizures. Dis. Nerv. System, 21: (Suppl.) 3, 57, 1960.

# TREE POLLINOSIS

## Effects of Single Annual Injections of Emulsified Extract in 560 Multiply Allergic Patients, XI.

ETHAN ALLAN BROWN
M.R.C.S., (England); L.R.C.P., (London)
Boston, Massachusetts

THERE are many reasons why there are so few studies of tree pollinosis. The dates on which the symptoms occur depend on the variations of the weather of late March through early June, a time when one-third of the annual precipitation falls. Unless he is afflicted with other types of allergy or is multiply allergic to the tree pollens themselves, the patient who is sensitive to only one or two of the pollens is bothered for some of the time and for only fifteen to thirty days. The patient who is allergic to all of the important tree pollens may suffer for as long as fifty or sixty days, although intermittently so. When he is not allergic to other substances for which treatment is needed, a patient will not, for so small an amount of discomfort, subject himself to weekly injections for almost all of the first year during which he must take injections of unemulsified extracts.

Because of the variations in degree of the affliction, its duration and the irregularity of its occurrence, few patients will remember from year to year that a recurrent disorder has affected them. This is especially true because of the concomitant prevalence of the Spring type of upper respiratory tract infections. Some patients will report only that each Spring they suffer from "colds," but by history and tests, it is discovered that the patient has been mistaken.

Patients allergic to molds may equally well be allergic to tree pollen. Those allergic to grass pollen may, despite excellent treatment, only suffer from their allergy when both the tree and grass pollens are ambient and do well after there are no tree pollens in the air.

Many of the patients included in the present study knew of their allergy to grass pollens, but did not know that they were also allergic to the later appearing tree pollens. Observation for a period of several years corroborated the diagnosis of their tree pollen allergy.

Additional studies done for a period of more than ten years proved that the obverse picture of what has been presented was also true. Patients who were predominantly tree pollen sensitive were then, by the same type of annual supervision, discovered to be allergic to grass or ragweed pollens, or both, although less severely afflicted by these other seasonal or environmental allergens for which treatment by means of a single injection of emulsified extract was also available.

There were, then, the patients whose predominant allergy was to the tree pollens but who suffered from lesser degrees of discomfort from other

seasonal microspores. There were patients who reported for treatment for grass or ragweed pollinosis, or for other mold allergy but who were discovered to be allergic as well to tree pollens. There were other patients whose clinical histories were those of perennial symptoms but who suffered exacerbations at the peaks of each of the three pollination periods and included were those of the trees.

When it became known that a disorder which was considered to be a prolonged nuisance rather than a disaster could effectively be controlled by a single injection of emulsified extract, many patients who had never previously looked for treatment requested their physicians to refer them for what appeared to be a worthwhile method of obtaining relief.

Any practicing allergist who searches, as we have, for tree pollen sensitive patients will be agreeably surprised at how many he will discover. He will have no difficulty in matching the number (560) here reported upon.

## THE PROBLEM OF TREE POLLINOSIS

The magnitude and the teleological problems of tree pollinosis are complex. There have been recorded in the United States 805 species of native trees. At least ninety additional species have been imported and have escaped from cultivation subsequently to become naturalized. Because trees are imported for special purposes, as for example, for specimen purposes in an arboretum, there is no exact tally of the numbers of all types of trees to which allergic patients may be exposed.

There are, in New England, 30,851,000 acres of forest land, or one-third of all the land area of the six states. In the South, half the land represents forest, and in the West, five-sixths. The trees which line city streets are not counted.

As far as is known, the first study of the trees and of their characteristics was made by Theophrastus of Ereus (372-287 B. C.) and 2,000 years later, Linnaeus (1707-1778) wrote his classical work on terminology. No data useful to us, however, was printed until James G. Cooper, in 1859, wrote a paper, "On the Distribution of the Forests and Trees of North America." In 1897, "Silva of North America" by C. S. Sargent was published. It comprises fourteen volumes and a total of more than 2,100 pages and 740 plates. In 1899, Henry Solon Graves published his "Practical Forestry in the Adirondacks." There appeared by Frederic E. Clements, in 1909, "Plant Formations and Forest Types." In 1924, Carlos G. Bates described the "Forest Types in the Central Rocky Mountains." Not until 1931 did Gustaf A. Pearson print his great work on "Forest Types of the Southwest United States."

Although printed in 1924, the best available "tree map" of the country is that of Homer L. Shantz and Raphael Zon. There is no available publication which shows the distribution of all of the trees of the United States, because in some areas either the botanical explorations have been

less than thorough or else have not been complete. Those explorations which have proven to be satisfactory have not all been interrelated with the specimens collected in each of the great herbaria. My own explorations have shown isolated stands of moderate size not as yet listed anywhere.

### BOTANICAL RELATIONSHIPS OF THE TREES

The family interrelationships of the trees and of their pollens are not generally known. Few have ever been studied by passive transfer or other available techniques. The oaks, of which there are between 250 and 500 species, belong, for example, to the family of Beeches and are also related to the Chestnuts. The intermediate species, the Tanbark Oak, resembles a Chestnut tree but bears acorns. The Pines include the Junipers, Cedars, Spruces, Firs, Larches, Hemlocks and Sequoias. The Hornbeam, although named Blue Beech, is a Birch, as are all the species of the American Alders. The Aspens and Cottonwoods are Willows. The so-called Willow Oak, however, like other oaks belongs to the family of Beeches.

The Maples are well defined except for the fact that the family includes the Box Elder. Hickory, the latest appearing of the tree pollens, is a member of the Walnut family. In New England, the White, Black and Red Ash trees are members of the species of Olives. The Mountain Ash resembles a Cherry but is truly a member of the Rose family, as are the 125 species of Hawthorn. Among other complexities, it must be remembered that the Palmettos are related to the grasses.

Any of the insect pollinated trees can shed pollen into the wind and may cause as much difficulty as can those trees which are truly anemophilous.

Lack of space makes it impossible to touch more than the fringe of the subject of tree pollinosis, but a study extending over a period of more than two decades has proven tree pollinosis to be a complex aspect of allergy. In our present practice, almost 20 per cent (rather than the usual 10 per cent) of the allergic patients treated are affected to some degrees by the pollens of the trees. Our experience has consistently duplicated the studies of Wodehouse who, in 1933, reported that during May the combined pollen counts were higher than at any other time.

### FIRST STUDY

For the initial and exploratory investigation[1] a small group of 164 patients was selected. No matter what other tree pollen extracts elicited positive skin test reactions, each patient, because of the botanical interrelationships of the tree pollens, received (in accordance with tradition) an injection of equal parts of extracts of Birch and Oak pollens. The period of administration extended from December 10, 1957 to February 5, 1958. The doses ranged from 1,700 to 10,000 P.N.U. (Protein Nitrogen Units), although thirty-seven, sixty-seven and fifty-four patients, respectively, received 1,700, 3,300, and 5,000 P.N.U.

Nineteen patients reported symptoms, and of these, fifteen were concomitantly allergic to grass pollen. In six of the nineteen, the greater part of their difficulties appeared during the overlapping of the tree and grass seasons. The symptoms of nine patients were recorded as occurring during the early Spring. In three others similarly affected, positive test reactions to the pollens of the grasses were elicited when they were tested late in May. None of the patients, however, had been tested with mold extracts or had been studied for allergy to the known "X" or "Y" factors of Summer or Autumn.

Because there were included in the study eighty-nine patients in transition from the multiple visit type of treatment to the single enapothetic injection, the conclusions were not considered to be final. The paper was published because of its sequence in a series of studies of greater over-all importance.

## SECOND STUDY

Because of the knowledge acquired from the first and other studies, the second investigation[2] embodied a different experimental pattern. Of the 164 patients previously treated, 139 received a second annual injection. Included also were 155 patients who had never before received any injections of tree pollen extract. In those patients in whom the symptoms extended beyond the reported period of tree pollination and in whom positive test reactions to grass pollen extract could be elicited, an injection of both tree and grass pollen extracts was administered. The fifteen patients who had developed symptoms following their first injections of tree pollen and were thereafter treated for both tree and grass pollen sensitivity, suffered not one sneeze throughout their second year of treatment. The results may have been due, in part, to better protection for their tree pollinosis.

For control purposes, the supposedly unimportant extracts of Alder, Beech, Maple, Ash and Hickory pollens were omitted. The patients were informed that some days of symptoms might occur, but were not told of the probable dates, although these could only be generally determined. A control group of approximately 500 patients was maintained on traditional programs of injections of unemulsified extracts, given according to the usual schedule of doses.

There were other changes in treatment. When a better emulsion became available in that the droplets were smaller, all amounts administered were greater, regardless of the patients' reactions to the tests then performed. The new emulsion caused not one systemic reaction. When we applied more rigid criteria, we found that thirty-six of 379 patients (as compared to nineteen of 164) experienced symptoms. The results are better than they appear to be at first sight because, as noted, 155 patients had never before received treatment.

## CURRENT STUDY

For the present (third) investigation, the number of patients treated was increased to 560. Of these, 124 had previously received two of the annually administered injections, and 204, one injection. It is clear that the clinical progress of 328 of the patients had then been followed for two years.

TABLE I. PATIENT POPULATION ACCORDING TO THE NUMBER OF INJECTIONS OF EMULSIFIED EXTRACT

| | First Injection | Second Injection | Third Injection | Total |
|---|---|---|---|---|
| Number of patients | 232 | 204 | 124 | 560 |

The number of patients who were first treated in 1959, however, includes those patients who had been used as controls for multiple visit injection programs because of their ragweed pollen sensitivity. Their maintenance dose had been administered at intervals of four to six weeks. When they discovered their sensitivity to tree pollens, they did not wish to return to a program of weekly injection for one group of pollens and an injection every four to six weeks for the other. They were eager to have one injection of emulsified tree pollen extract, although some continued the traditional treatment for their ragweed pollinosis. Their satisfaction with their symptom-free season was the deciding factor in their transition to treatment with injections of emulsified extract.

The population, then, includes five types of seasonal and perennial allergy. Some patients are chiefly allergic to either of the two types of pollens, those of the Spring and Fall; and though they are less affected by one or the other, they are not allergic to the grass pollen. Other patients, who are treated either with tree or grass pollen, are afflicted only when both pollens are ambient or supervenient or when exposure is therefore great. The third group is represented by patients whose symptoms begin in April, continue with no abatement until late July, and recur in late August and last through September and October. Of these patients who reported no relief before treatment, although there were prolonged spells of rainy weather, 102 reacted to tests for molds. Finally, there were patients who were allergic only to tree pollens.

In order to make as certain as possible that symptoms of viral infections of Spring and early Summer would not confuse the clinical picture, 336 of the patients received two successive injections of Influenza Viruses A, A' and B, given in doses of 125 CCA and 50 CCA Units. Children received vaccines of Adenoviruses 3, 4 and 7†, of which each dose was 50 CCA Units emulsified in 0.5 ml of Arlacel A-Drakeol 6VR. The interval between injections was based on the patient's convenience and

†Resprogen, Parke Davis & Co.

ranged from three weeks to three months and occasionally longer. The Influenza Virus injection was usually administered at the same time as an injection of pollen, molds or house dust extract. Because of the high degree of emulsification, egg sensitivity, no matter how great, was ignored. There were no local or systemic reactions.

Patients who had been completely well for a two-year period were not only permitted, but actually encouraged to forego treatment to discover how long the injection of emulsified extract would protect them. However, there were the usual number of patients who left our area or ceased treatment for financial or other reasons such as pregnancy or parturition. Some went to distant schools and could not leave at the time that the injections should have been administered. An almost equal number of patients (232 as compared to 228) were chosen for first injections.

### TYPES OF MULTIPLE ALLERGY STUDIED

The observation period of one to three years specifically showed, as previously noted but only generally, that the patients predominantly allergic to tree pollens suffered extraseasonally from grass, Plantain and ragweed pollens, molds, house dust, and animal danders.

TABLE II. CLASSIFICATION OF THE PATIENT POPULATION ACCORDING TO CLINICAL ALLERGY
(In Addition to Tree Pollinosis)

| Concomitant Types of Clinical Allergy | House Dust | Grass Pollen | Molds | Ragweed Pollen | Others (Plantain, Pollen or Danders) | Influenza Viruses |
|---|---|---|---|---|---|---|
| Number of patients | 317 | 481 | 102 | 500 | 80 | 336 |

During the Spring and Fall, the patients listed suffered from the usual types of viral infections. It will be noted from the second table that 500 patients are listed as allergic to ragweed pollen. This includes the patients whose symptoms are severe in the Spring and mild in the Fall, and those whose symptoms are severe in the Fall and mild and intermittent in the Spring.

TABLE III. PATIENT POPULATION DISTRIBUTED ACCORDING TO AGE AND SEX

| Years | 3-5 | 6-10 | 11-20 | 21-30 | 31-40 | 41-50 | 51-60 | 61-70 | 71-74 | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| Males | 3 | 32 | 120 | 49 | 52 | 37 | 20 | 12 | 2 | 327 |
| Females | 1 | 18 | 47 | 46 | 44 | 46 | 27 | 4 | 0 | 233 |
| Total | 4 | 50 | 167 | 95 | 96 | 83 | 47 | 16 | 2 | 560 |

### POPULATION TREATED

The patients studied varied in age from three to seventy-four years, and, as previously reported, there was a male predominance. No degree of success or failure in treatment could be related to sex, although because

of outdoor sports, the younger males probably faced greater or more frequent exposure. The older female patients were similarly exposed because of gardening.

Exposure seemed to make little, if any, difference in the results, particularly because all patients were encouraged to test the effects of treatment to the absolute limit. They were permitted to mow lawns, play golf, and risk all types of massive exposure. Although a number reported that they could sniff the pollinating plant with no adverse reaction, the practice was discouraged because other pollens, for which the patient had not been treated, might be inhaled in such quantities as to cause symptoms.

TABLE IV. DISTRIBUTION OF PATIENT POPULATION IN ACCORDANCE WITH DISORDERS AND THEIR DURATION

| Years | 3-10 | 11-20 | 21-30 | 31-40 | 41-50 | 51-60 | 61 or More | Total |
|---|---|---|---|---|---|---|---|---|
| Number of patients with bronchial asthma | 20 | 50 | 16 | 11 | 16 | 12 | 4 | 129 |
| Number of patients with allergic coryza | 10 | 51 | 43 | 36 | 25 | 19 | 4 | 188 |
| Number of patients with bronchial asthma and allergic coryza | 14 | 44 | 26 | 40 | 35 | 13 | 10 | 182 |
| Number of patients with other disorders | 10 | 22 | 10 | 9 | 7 | 3 | 0 | 61 |
| Total | 54 | 167 | 95 | 96 | 83 | 47 | 18 | 560 |

## DISORDERS TREATED

We know from Table IV that 188 patients were treated for their allergic coryza. The usual concomitant symptoms affected the conjunctivae, the palate and the internal ears. One hundred and twenty-nine patients had no symptoms localized in the upper respiratory tract, and their pollinosis resulted in bronchospasm. Some of these patients had previously noted symptoms of allergic coryza, but rarely of allergic conjunctivitis.

In contrast, 182 patients suffered from both hay fever and asthma, the former often occurring earlier in the season. Some patients experienced bronchospasm only after massive or long exposure, as, for example, during long automobile trips. In sixty-one patients, the symptoms chiefly affected the conjunctivae, the larynx, or the pharynx, or were seasonal and caused exacerbations of atopic or eczematoid dermatitis.

No patient was treated solely on the basis of a positive cutaneous or conjunctival test. On the contrary, in patients in whom such positive test reactions occurred, but the clinical picture was not clear, no injection was administered until observation had proven the clinical counterpart of the test reaction to be present. In other words, no subject of this particular population received prophylactic treatment. Also, none of the skin-test and eye-test negative patients with seasonal symptoms was included in this study. These will be subjects of separate reports concerned with what may be termed X and Y Factors, two types of seasonal allergy which are thought occasionally to be associated with, but sometimes not at all related to pollinosis.

### DURATION OF DISORDERS TREATED

From Table IV, it will be noted that no patient was accepted for treatment unless he had suffered three successive years of symptoms. There were fifty-four patients whose symptoms had been present from three to ten consecutive years, but those whose disorders had been present for ten to twenty years numbered 167. For the successive decades, there were ninety-five, ninety-six, and eighty-three, the numbers following the general population curves. Forty-seven patients had experienced their disorders for fifty-one to sixty years. Only eighteen had been afflicted for more than sixty years.

Some of these patients could remember when the only treatment available to them were injections of strychnine, serum from inoculated horses or cows, oral preparations of iron, and local treatment with cocaine and its derivatives. The records of some show them to have been treated by arsenic, ketogenic diets, injections of sulfur in oil, typhoid vaccine, and autohemotherapy.

The sixty-five patients who had been afflicted for more than fifty years (Table IV) had been treated by the multiple visit programs without substantial help. It is interesting to note from the Protocols that only two of these patients reported symptoms and in both cases, they were mild.

TABLE V. SPAN OF PERIOD OF TREATMENT

| Month | December | January | February | March | April | Total |
|---|---|---|---|---|---|---|
| Number of patients | 215 | 255 | 41 | 16 | 33 | 560 |

### DOSE OF EXTRACT ADMINISTERED

The investigation was planned so that the patients would receive either 1,000, 3,000, or 5,000 P.N.U. Those patients who reported during the first months of Spring needed quicker effects and shorter periods of protection. No matter what their degree of skin test reactivity, seventy-two of these were injected subcutaneously with doses of 1,000 P.N.U. or less, usually in 0.5 ml. Those patients who were suffering from the effects of other allergens at the time of the proposed injection were, for purposes of caution later discovered to be unnecessary, given doses of 2,000, 2,500, or 3,000 units. This group totaled 103. Fifty-two patients received 4,000 P.N.U., but 333 patients took a single injection in one site at one time of 5,000 P.N.U., regardless of the skin test response or the patient's clinical history.

No epinephrine was added to the extract injected in emulsified form. However, those patients who planned to leave the office and to travel some distance by plane, train or car were protected by an injection of 0.1 ml of long-acting epinephrine (Susphrine, Brewer), given subcutane-

ously just before or after the injection of extract was administered. No patient is asked to wait after his injection because with today's stabilized emulsions, no local reaction or immediate systemic effects occur. For the benefit of visiting physicians, patients who live nearby have been asked to return six to eight hours later the same day and occasionally the next day so that it can be demonstrated that the site of the inoculation is not palpable.

TABLE VI. DOSES OF EMULSIFIED EXTRACT ADMINISTERED AND NUMBER OF PATIENTS TREATED WITH EACH

| Dose (P.N.U.) | 250 | 500 | 600 | 1000 | 2000 | 2500 | 3000 | 4000 | 5000 | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of patients | 7 | 4 | 1 | 60 | 22 | 10 | 71 | 52 | 333 | 560 |

## SKIN TESTS

Studies now in preparation for publication will demonstrate the unreliability and inconsistency of the degree of magnitude of either the skin or eye test reactivity. The seventh table is therefore included only for purposes of comparison.

The difference in the test solutions from those used in previous studies is represented by the range of the dilution and concentrations of the extracts. Pressure puncture tests were done with extracts of successive strengths of 10,000, 20,000 and 40,000 P.N.U./ml. Solutions for intracutaneous tests were successively 100, 1,000, 2,000, and 4,000 P.N.U./ml. But as the studies were in progress and to save the patients' time and effort, the more concentrated extracts were often used as first test solutions, although the patients might have been reactive to more dilute extracts. The response to the skin test is not considered to be important. The injections of emulsified extracts are based not on the results of such tests, but on the patient's clinical sensitivity. However, patients who were suspected of being more clinically sensitive or who had never previously been treated or tested, were, as a matter of interest, tested with more dilute solutions. But studies have shown that the skin test reactions are such unreliable determinants of a patient's dose tolerance that should the first dose of multiple visit programs be based solely on this reaction, such programs obviously rest on false premises. For example, Table VII should not lead to a conclusion that the patients were "less sensitive" because of the reactions to the stronger solutions to which they were tested.

Many of the patients listed as reactive at the 4,000 P.N.U./ml level presented clinical histories of hypersensitivity and suffered from the earliest to the latest days of pollination. Other studies showed us that patients who had been abroad for a period of years and were not exposed to the pollens which had caused symptoms before their sojourn, often demonstrated smaller skin test reactions than before they left the country.

However, re-exposure to pollen caused a reappearance of symptoms. The skin tests done in new patients during the season of affliction were invariably larger than those done in the same patients when they returned for their injections, often eight months later.

Some patients, under study for some years and skin-test negative, showed their first positive reaction to a skin test only during the season itself. In other patients, who were tested annually for a period of twenty-five years, the test reactions could not be related consistently to the clinical history, although these might show a decreased response and sometimes become skin-test negative. With greater exposure or for other reasons, the symptoms might return and concomitantly a larger skin test reaction, as determined by titration tests. There were other patients in whom the test reactions actually increased for some years, and then later, during the same year, decreased in size. The intensity of the reaction could not, therefore, be related to the strength or the age of the solution used for the test. The other variables discovered to be present and known for some time to characterize skin tests will be the subject of a separate report.

Traditional techniques of determining the dose were followed only for the first studies, because treatment with emulsified extracts was considered to be a modification of multiple visit programs and not a new type of treatment subject to its own laws and consistent within itself. When emulsions were prepared in such a manner as to include no unemulsified extract or with present-day emulsified extracts, the dose is not at all related to the size of the skin test reaction, but to other factors, which will also be the subjects of separate reports.

TABLE VII. POPULATION OF PATIENTS STUDIED DISTRIBUTED ACCORDING TO SKIN TEST REACTIVITY

| Testing solutions in P.N.U./ml | P.P.P. | 100 | 1000 | 2000 | 3000 | 4000 | Total |
|---|---|---|---|---|---|---|---|
| Number of patients | 98 | 41 | 61 | 225 | 1 | 134 | 560 |

## THE EXTRACT

It became apparent as successive studies were completed that it might be wise to treat patients allergic to tree pollens with Elm pollen extract. We also decided to treat patients who suffered mild symptoms in the early Spring with extract of Alder pollen. The extract of Beech pollen was included in the treatment of patients who lived in areas characterized by large stands of Beech trees.

The preparation of the extract has been described.[3] The pollen is not defatted and the presence of the pollen oil can be demonstrated to result in a better emulsion. The extract is described throughout this communication as standardized in Protein Nitrogen Units (P.N.U.), although the concentrations will be described otherwise in the thirty or more papers to be published.

### THE EMULSION

The results of studies with the so-called 1:9:10 emulsion have been published. When the emulsion is prepared with Arlacel A and mineral oil, it is stable as shown by visual tests, physical properties and experiments in animals. The droplets have been photographed.

With the use of a 132 N.A. plano apochromatic immersed objective, an immersed aplanatic substage condenser and blue daylight filter, carbon arc photomicrographs at 1300 diameters can be taken of fields in which some of the droplets are proven to be out of focus, on separate planes and, therefore, not flattened by the cover glass. Additional magnification, 10X, can be obtained by special screens. All measurements are made with a calibrated filar micrometer eye piece. A number of types of emulsions have been studied in this manner. That used for the present study is currently prepared quite differently and will be the subject of a separate report.

For the patients described in this study, the emulsion labeled "D" was used. Its characteristics are listed, although it has been improved. The droplets are of a diameter of 0.1 $\mu$. Larger droplets were not found in each field, but when discovered, the largest measured droplet was of a diameter of 4.5 $\mu$.

The size frequency curve was radically skewed with a high peak and a low curve representing few droplets of the larger size. Obviously, because it takes a great number of small droplets to equal the volume of the uncommon large droplet, the average size is represented by a diameter of 3.1 $\mu$, as derived mathematically from $dy = \frac{\varepsilon nd^4}{\varepsilon nd^3}$. This, of course, will mislead the casual reader. The term "mislead" is used because in this frame of reference an "average" is not a pertinent feature of the emulsion, especially because for test purposes, a "D" preparation had been allowed to stand at room temperature and had been sent to the laboratory by surface mail. It was, therefore, exposed to outdoor temperature variations for several days of the three weeks which elapsed between preparation and examination. It was not re-emulsified before the diameters of the droplets were measured. In practice, the emulsion is prepared, and the amount of time that elapses between preparation and injection into the patient is no more than it takes to load a syringe and walk several paces. From a physical point of view, if kept refrigerated, the emulsion is quite stable for periods of up to one year. The extract, that is, the droplets surrounded by oil, is very stable.

The magnitude of the surface area involved for a droplet of diameter of 0.1 $\mu$ ($r=0.05$ $\mu$) must be known to be appreciated. When the dispersed aqueous phase represents 0.5 ml for a total injection of 1.0 ml of the preparation, if "V" represents the total volume of the dispersed phase; "v," the volume of one drop of the same phase; "r," the radius of the drop; "n,"

the number of droplets of radius "r" in total volume "V"; and "a," the interfacial area of one droplet, then "A," the total interfacial area of the dispersed phase is:

$$V = 3.00 \times 10^{13}\ \mu^2 \text{ or } 300{,}000\ \text{cm}^2.$$

For investigators who wish to study their own emulsions, the necessary mathematical steps are:

$$V = 4\ \ r^3$$
$$n = V/v = 3V/4\ \ r^3$$
$$a = 4\ \ r^2$$
$$A = nxa\ \ = 3V/r$$

During the progress of the study, we learned to prepare emulsions of better quality. The diameter of the smallest droplets remained at 0.1 $\mu$, but by means of two emulsifying agents, two oils, and a change in the proportions of the ingredients, the largest droplets which could be discovered in no matter how many fields were no greater in diameter than 1.8 $\mu$. The average droplet diameter again (subject to the qualifications noted) became 1.1 $\mu$. The emulsions have since been prepared with droplets of smaller diameters and with characteristics of greater uniformity. The factor of safety has been increased, but the immunological effects of such emulsions have not, as yet, been fully determined. From the point of view of safety, however, the E'T emulsion has permitted us to administer without reaction more than 5000 injections and in such patients in whom the doses varied from 600,000 to 2,500,000 multiples of the amount which had previously been the cause of systemic reactions when the same patients had been given unemulsified extract.

Although the data presented may not appear to be pertinent, corroborative studies must nevertheless be based on the use of emulsions of the same type proven to remain stable in the animal body or in humans. Studies done with emulsions with which positive skin test reactions can be elicited and which have been prepared by several passages back and forth between two 10 ml syringes may appear to look like emulsions, but do not represent more than temporary dispersion of some of the aqueous in some of the oily phase. These crack at room temperature and even more quickly when injected into sensitive patients. Not only is the reaction rate following the use of such apparent emulsions high, but the protection is low because of the rapid absorption and excretion of the unemulsified extract contained.

## METHOD OF ADMINISTRATION

In previous studies, mention was made of the fact that the injected material must be placed subcutaneously in such a manner as to avoid slashing deep capillaries or larger vessels, whose courses run along the more superficial layers of the muscles. Faulty technique is the basic cause of many of the systemic reactions experienced in the administration of unemulsified extract. Proper technique leaves only the irreducible, minimal number of reactions associated with any injection of any medicinal substance.

The worst reaction, an accidental back seepage which may also be avoided by proper technique, results only in a flush reaction in no more

than one patient in 5000. The number of reactions described by other investigators and the fear of systemic effects so often expressed, especially by those unfamiliar with the enapothetic type of treatment, are due more often to faultily prepared mixtures of emulsified and unemulsified extract and most frequently to the method of placing the mixture in what is thought to be the subcutaneous tissues. When the physician knows truly how to administer subcutaneous injections, large doses of unemulsified extract can safely be given to sensitive patients. When the extract is properly emulsified, the "problem" of safety is no longer a problem.

## RESULTS OF TREATMENT

Of the population of 560 patients, only twenty-eight reported the presence of any symptoms whatsoever. If percentage figures will help to clarify the picture, these patients represent 5 per cent of those treated. The results, however, are better than they would appear at first glance. One patient allergic only to tree pollens reported having suffered mild symptoms of allergic coryza for all of April and May. He was not treated with all the extracts of the tree pollens to which he showed positive skin test reactions. Additional studies are to be done to uncover other seasonal or environmental causes, but at the moment, this patient represents the only true failure, despite a dose of 5000 P.N.U. of the tree pollen extracts used.

None of the patients previously treated and reported as being afflicted by overlapping pollen seasons suffered from one sneeze or wheeze. All, in accordance with knowledge acquired from the preceding two studies, had been given injections of tree and grass pollen extracts.

One patient, allergic to tree pollen and to the more common molds of New England *(Alternaria Tenuis, Helminthosporium Interseminatum,* and *Hormodendrum Cladosporioides),* was not certain of the effects of warm, damp weather. She received a total dose of 1000 P.N.U. of the tree pollen extracts and reported on May 5, 1960, the appearance of conjunctival symptoms, nasal stenosis and coryza. But these occurred also during some spells of dry weather. Were her symptoms subsequent to low dose or to exposure to molds? I do not know.

Another patient, allergic clinically to tree and ragweed pollens and to house dust, received a small dose of 1000 P.N.U. of the mixture of tree pollen extracts. He reported on June 28, 1960, that mild symptoms had occurred during May. This patient and several others may have been treated with too low a dose or other pollens or molds may have been present during the one month period.

We know from ancillary studies that there are two factors, "X" and "Y." Neither is related to pollen, and the first is ubiquitously present in New England from May to late September. Some of the patients suffered from tree pollinosis and were skin-test reactive to X-factor. This will not be used as an excuse or a reason for the presence of their symptoms until additional studies by gel diffusion techniques have been completed. In the

future, all patients in whom symptoms occur despite adequate treatment will, when reactive, for their second injection receive the relevant factor. Obviously, any study which does not take these factors into consideration is not complete as regards the response to treatment with any type of emulsified or unemulsified extracts.

TABLE VIII. DISTRIBUTION OF PATIENTS WITH SYMPTOMS AND IN ACCORDANCE WITH ASSOCIATED SENSITIVITIES

| Category | Number in Each Category |
|---|---|
| T | 1 |
| T, M | 1 |
| T, R | 2 |
| T, G, D | 2 |
| T, R, D | 4 |
| T, G, R | 2 |
| G, R, M, D | 3 |
| T, G, R, D | 5 |
| T, G, R, M | 2 |
| T, G, R, P, D | 2 |
| T, G, P, R, M | 2 |
| T, G, R, P, D, M | 2 |
| Total | 28 |

Legend: M—Molds; T—Tree Pollens; P—Plantain Pollens; G—Grass Pollens; D—House Dust; R—Ragweed Pollens.

The other twenty-five patients who reported symptoms defy any practical classification. As will be noted, all were known to respond with typical allergic symptoms to exposure to a number of inhalant substances, and in many cases, to the ingestion of foods. They could not receive treatment for such foods or for Cottonseed, Castor Bean (in a stevedore), Pyrethrum (in an exterminator) and feathers (in a salesman of furniture). Elimination of these substances could not always be complete, granted that part of the regimen represented freedom to engage in all activities except those which obviously were associated with immediate and severe symptoms. The major seasonal allergens, that is, the pollens, and the environmental and seasonal allergens such as house dust and molds to which they were allergic are listed in the eighth table.

The twelve categories listed represent an oversimplification and because of other associated types of allergic responses do not, of themselves, enable us to see all of the parameters involved. Some of the patients are clinically allergic, as noted, to animal danders, foods, and to particular environments from which the causative allergen cannot be isolated or else because the complexity and number of allergens present defy complete analysis. One patient, a farmer, hays and possesses cats, dogs, horses, cattle and poultry. But, also exposure to specific types of feed for some of these animals brings on symptoms. A long stay in the barn is followed by bronchospasm. He

can only leave his farm infrequently and can only be treated for the major injectable allergens. He does need occasional prophylactically or therapeutically prescribed antihistaminic agents or antispasmodic drugs. He is included in the present paper only because, as with the other patients, his symptoms occurred during the tree pollen season. They might well have been caused by any number of other allergens coincidentally present.

### IS THE DOSE ADMINISTERED A FACTOR?

Of the seventy-two patients who received a dose of 1000 P.N.U. or less, five reported symptoms, and of the ten who received a dose of 2500 P.N.U. two patients also reported symptoms. From Table VI, it is clear that seventy-one patients were treated with 3000 P.N.U., and seven of these suffered from some difficulty. Only one of the fifty-two patients who were treated with a dose of 4000 P.N.U. and fourteen of the 333 who were treated with 5000 P.N.U. reported symptoms.

It is clear from the same table that all the levels of the total dose are represented, although not equally. If we take as an example the fact that five of sixty patients treated with 1000 P.N.U., and if extrapolation is valid in so small a population, then more than five times as many of the patients treated with 5000 P.N.U. should be affected, namely twenty-five to thirty. But only fourteen of these patients, as previously noted, reported symptoms.

Only one of fifty-two patients who received 4000 P.N.U. registered symptoms, as did seven of seventy-one who were given a dose of 3000 P.N.U. This latter number, however, is so close to five of sixty patients referred to above that it would seem there is little difference in effect between doses of 1000 and 3000 P.N.U. There is evidently a threshold dose above 3000 P.N.U. which is associated with greater freedom of symptoms and in greater numbers of patients, although the significance of this conclusion may be questioned, again because the numbers are so few.

In regard to numbers, however, the present and past studies of tree pollinosis cannot be the subjects of comparison, because the extracts represented more pollens and many of the doses administered were higher, although some of the patients previously treated had been given higher doses, for example, 10,000 P.N.U.

### IS THE DATE OF ADMINISTRATION A FACTOR?

All of the patients who received 1000 P.N.U. were treated between December 24, 1959 and February 2, 1960. Lack of lasting protection may have affected the results, but then there are the usual exceptions. One patient who was treated on April 27, 1960 with 2500 P.N.U. also reported symptoms. Was the date of administration in his case too late?

Those patients who, after a dose of 3000 P.N.U., reported some symptoms, were treated between December 17, 1959 and February 24, 1960. Again, was the dose too small and was the date of administration too early? Of the fourteen patients who received 5000 P.N.U., twelve took their injec-

TABLE IX. CHARACTERISTICS OF PATIENTS WHO REPORTED SYMPTOMS

| No. | Disorder | | Years of Duration | Other Clinical Sensitivity | Dose P.N.U. | Date Given | Dates or Times of Symptoms | Comment |
|---|---|---|---|---|---|---|---|---|
| | AC | BA | | | | | | |
| 1 | X | | 6 | None | 5000 | 1- 6-60 | Two weeks in Spring | Symptoms mild. No medication required. No symptoms 1958, 1959 |
| 2 | | X | 17 | Molds | 1000 | 1- 6-60 | 5-5-60 | Symptoms mild. Controlled with antihistaminic agents and not needed for mold sen. |
| 3 | X | | 10 | ? Molds Ragweed | 3000 | 1-28-60 | 6-2-60 6-9-60 | Late tree pollens. ? Mold allergy. (Symptoms only in damp weather). |
| 4 | X | | 6 | ? Molds ? Grasses ? Ragweed | 1000 | 4- 7-60 | 5-30, 31, 6-1-60 | Late dose? Late for injection of grass pollen and mold extract. |
| 5 | | X | 14 | Grasses Ragweed Dust | 3000 | 12-17-59 | Mid-May to mid-June | Low dose? ? Early injection. ? overlapping seasons? |
| 6 | X | | | | 3000 | 1-13-60 | May | ? Low dose. ? Early injection. ? Overlapping seasons. |
| 7 | X | | 5 | | 3000 | 1-31-60 | 5-15-60 6-10-60 | ? Low dose. ? Early injection. ? Overlapping seasons. |
| 8 | X | | 20 | Grasses Ragweed | 1000 | 2- 2-60 | Dry, windy days. | ? Low dose. ? Early injection. Overlapping seasons. Not treated for all tree pollens. |
| 9 | | X | 2 | Grasses Ragweed Dust | 5000 | 1-14-60 | 5-21-60 to 5-28-60 | Early injection. ? overlapping season. |
| 10 | X | | 7 | Grasses Ragweed Dust | 1000 | 12-29-59 | 5-12-60 to 5-22-60 | Early injections. ? Low dose. ? Allergic to foods. |
| 11 | X | | 5 | Grasses Ragweed Dust | 5000 | 1- 6-60 | Symptoms while at work | Plumber—exposure to dust. Early injections. Effects of other tree pollens. |
| 12 | X | X | 25 | Grasses Ragweed Dust | 5000 | 12-29-59 | Symptoms only in damp weather | Mold allergy? ? Early injection. Also, allergic to feathers, other inhalants. |
| 13 | X | X | 30-15 | Grasses Ragweed Dust | 3000 | 1-28-60 | April and May | Allergic to cat, cattle danders, pyrethium. Early injection, ? low dose. |
| 14 | X | | 8 | Grasses, mold, ragweed, dust | 5000 | 12-17-59 | 31 days as of May 23, 1960 | Early injection? ? Molds, grass pollens. |
| 15 | X | | 2 | Grasses, mold, ragweed, dust | 3000 | 2-24-60 | Symptoms began 5-5-60 | ? Molds. ? House dust. ? Other sensitivities. |
| 16 | X | | 5 | Grasses, mold, ragweed, dust | 5000 | 12-22-59 | March | Early injection? ? Molds. |
| 17 | | X | 12 | Grasses Ragweed Molds | 5000 | 2- 4-60 | 5-16-60 to 6-16-60 | Overlapping seasons? |
| 18 | X | X | 21 | Grasses Ragweed Molds | 5000 | 12-17-59 | Mid-May, damp weather | Early injection, ? molds |
| 19 | X | | 50 | Ragweed Dust | 1000 | 12-24-59 | May | Low dose? ? Early injection. |
| 20 | X | X | 25 | Ragweed Dust | 2500 | 4-27-60 | 6-1-60- 6-16-60 | Late injection? ? Grass pollen. |
| 21 | X | X | 13 | Ragweed Dust | 5000 | 1-12-60 | May | Farmer. ? Other allergy, ? hay and danders, ? feeds. |
| 22 | | X | ? | Ragweed Dust | 5000 | 1-14-60 | First day in March | Cause of symptoms unknown. |
| 23 | X | | 16 | Grasses, ragweed pollen, dust | 4000 | 12-29-59 | 15 days, late in May | Also allergic to cottonseed, feathers. Symptoms while living in Baltimore. |
| 24 | | X | 50 | Grasses, ragweed pollen, dust | 5000 | 4-26-60 | All of June | Late injection? Other sensitivities to tree pollens. ? Foods. |
| 25 | X | X | 31 | Grasses Pollen Mold | 2500 | 12-15-59 | 21 days, began 5-15 | Molds? ? Plantain, grass pollens. ? Late injection. ? Overlapping seasons. |
| 26 | X | X | | Grasses, pollen, ragweed, dust | 5000 | 1-19-60 | All of May | Other sensitivities? |
| 27 | X | | 5 | Grasses, ragweed, dust, molds | 3000 | 1-13-60 | 4-15-60 to 5-18-60 | Symptoms in damp and dry weather. Needs injection for molds, Plantain, etc. |
| 28 | X | X | 43 | Grasses, pollen, ragweed, mold, dust. | 5000 | 12-17-59 | May | ? Early injections. Kopak and pyrethium sensitivities. ? Other allergy. |

tions between December 15, 1959 and February 4, 1960. Two other patients who reported some symptoms received 5000 P.N.U. They took their injections on January 6, 1960 and April 26, 1960. Of the first group of twelve, six patients received their injections in December, four in January and two in February. It may tentatively be concluded that with the type of emulsion injected, the larger dose may in part compensate for the early date of the treatment, but the greater amount administered later in the year leads to better results. Although there are exceptions, but not many, all of the studies again point to the validity of this conclusion. With emulsions which are absorbed more slowly, however, other studies to be reported upon show that the span of treatment may be widened and also that much larger doses can be injected with a safety which approximates the absolute.

If, in the light of present knowledge, we could repeat the study, all patients would have received higher doses of all the allergens present during the season. The dates of administration would have been limited to February and March for those more allergic to the earlier appearing pollens of the trees. For those patients allergic to Oak, the injections would have been limited to the days of April. It may be possible to follow this administration procedure for the projected fourth study of tree pollinosis.

### SYSTEMIC REACTIONS

No patient experienced either a local swelling or a systemic reaction. In none did the injection cause a nodule, a cyst or an abscess.

### PROTOCOLS

The general and specific characteristics of the patients and their types of allergy are classified in the protocols. Examination of the protocols indicates that the patients who reported symptoms were all multiply allergic excepting for one of the patients who is allergic only to the pollens of the trees and suffers from no extraseasonal symptoms. The others are sensitive to the pollens and also to the molds, and in some cases to danders, environmental inhalants, fumes and foods. In few did the symptoms occur in accordance with the patterns established by a detailed study of new patients. The dates on which these untreated patients were affected differed from those listed, although concomitant periods of affliction were, in some cases, recorded. When a treated patient reports being afflicted on a day or days when no one else, treated or untreated, suffered any symptoms, it may, in most cases be concluded that another allergen is at fault. One patient, for example, was discovered to have been exposed to a "plastic" with which he, on a new job, sprayed cars.

To explain away the fact that twenty-eight patients suffered symptoms, no advantage is being taken of the fact that some of these were treated early, some late, some with small amounts of extract, that some did not receive all of the tree pollen extracts to which the sensitivity existed,

and that others were not treated for the grass or the early appearing Plantain pollen (if present and a cause of symptoms) or molds. In 232 patients, the treatment represented the first year of injections, although some had taken and abandoned multiple visit injection programs some years ago, chiefly because it was, for them, ineffective. In any case, with the multiply allergic patient treated for some of his allergy, the problem will always arise as to the cause of his difficulties. For the second year of treatment, many of these secondary factors will have been eliminated or their effects will have been more accurately measured and allowed for, although they will, as usual, be reported as not having been treated with unqualified success.

## HOW VALID ARE THE DATA?

The question must and should always arise as to the validity of the data and the conclusions drawn. In allergic disorders, whether they be caused by inhalants or foods, we possess nothing less objective than the totally well patient. What are labeled as "objective findings" may be applicable in the field of hematology in which, for example, a deviation from the normal and a return to physiological levels may be measured. We have seen such patients who are obviously not well and yet not neurotic, as for example, during post-influenzal "asthenia."

In bronchial asthma, a predicted, three second vitalometer reading is certainly objective because when the air is not in the lungs, it cannot be forced into the cylinder. The readings may be sometimes less than they should be, but they can never, under any circumstances, be greater. In allergic coryza, we are left with what must be termed "ornithological" types of standards. In other words, if it waddles like a duck and its feet are webbed, and if it swims like a duck and dives like a duck and eats like a duck and quacks like a duck and looks like a duck, then it must be a duck. It might be a duck-billed platypus *(Ornithorhynchus anatinus)* of the order *Monotremata,* but unless the observer sees only the bill and from this attempts to identify an animal seen in Tasmania, the chances that it is not a duck are small indeed.

The patient may have suffered from conjunctivitis, epiphora, eyelid swelling, nasal stenosis, sneezing, coryza, anosmia, epistaxis and itching of the palate and internal ears and late in the season from bronchospasm during each year for fifty years. Following multiple visit programs, he suffers local and systemic reactions, and in addition needs antihistaminic agents and antispasmodic drugs which only partially relieve his disorder. He then receives 100 or more multiples of the same extract as administered by the same physician with no subsequent local or systemic responses and reports no symptoms whatsoever. The vital capacity previously lessened during the season remains at its normal levels. Provocative tests elicit no symptoms. The patient then defers treatment for one year, and the symptoms recur. A placebo is administered and the amount of medicine taken for symptoms does not lessen from that taken during the years of multiple

injection programs. An injection of the extract in emulsified form is administered, and in ten days the patient is again on the road to full health. It is now in fashion to label such procedures and results as "subjective." The patient looks well, feels well, and all tests, such as they are, prove no abnormality to be present. If we wish to use the ornithological type of test, we must conclude that he is well.

Before we use the term "subjective" for the results of treatment with emulsified extracts, we must remember that the standards for these are no different for the enapothetic type of treatment than are those used for the multiple visit programs. And, what is more, there are at least 400 other disorders which afflict human beings, and for these which range from the common cold to migraine and from angina pectoris to Werding-Hoffman's Disease, the diagnoses are less objective and the results of treatment, if any, more subjective. One may always ask by what objective standards are the results of the multiple visit programs judged? The same standards must be used for both groups of patients, namely those treated by traditional and those by modern methods, except that the criteria for the patient treated by single annual injections are so high that he is permitted no symptoms whatsoever, as caused by the pollen or inhalent substance for which the injection has been administered.

Allergic allergists should, subject to human frailty, represent an objective jury. To my knowledge, of the 197 treated enapothetically, only one has suffered from mild symptoms and only because he requested a smaller dose than that which we planned to give him. For the following season, despite a positive pressure puncture test at the 10,000 P.N.U./ml level he took, in a single injection administered at one time, a dose of 5000 P.N.U. and with neither a local or a general reaction.

When objective criteria other than those here listed become available for patients treated by multiple visit programs, they will be applied to the patients now treated by single annual injections for each allergen. Certainly the results obtained in the treatment by us and by others of more than 150,000 patients cannot lightly be set aside.

## SUMMARY

An unselected population of 560 multiply allergic patients was treated by means of a single annual injection of tree pollen extracts administered in emulsified form. Of the group, 232 patients received their first injection; 204 their second and 124 their third. Of these patients, 481 were allergic to grass pollen, although many suffered from pollinosis only during the period when both tree and grass pollens were present in the air. In 500 patients, there was an associated allergy to ragweed pollen, although in many the ragweed pollinosis was the lesser rather than the major complaint. Allergy to house dust was recorded in 317 patients, and eighty patients

were allergic to Plantain pollen and to animal danders, and 102 to molds. All clinical sensitivities were corroborated by every available type of test.

The male patients outnumbered the female. The patients with upper respiratory tract pollinosis numbered 188; with lower respiratory tract pollinosis in 129 and with total respiratory tract responses in the others, although both disorders were not always concomitantly present. Other seasonal allergy affected sixty-one patients.

The span of the period of injections extended from late December to late April. No skin-test negative patients were included in this study. But in those included, the size of the response with the solutions varying from the pressure puncture type of skin test with an extract of 10,000 P.N.U./ml to the intracutaneous test with a 4000 P.N.U./ml concentration was usually ignored because in treated patients it did not reflect the degree of clinical sensitivity.

Low doses (below 4000 P.N.U.) were administered to 175 patients. The others received doses of 5000 P.N.U.

There were no local reactions and no abscesses, nodules or swollen arms. There was not one systemic reaction and not one urticaria at the site of the injection.

Twenty-eight patients reported symptoms. One day of difficulty, although the reason might have been known, was sufficient for classification as a poor result. No patient previously proven to be allergic to tree and grass pollens and subsequently treated for both reported any symptoms. One patient allergic only to tree pollens and another to both tree pollens and molds both reported the symptoms described in the protocols. In such patients, further studies will be done to make certain that the symptoms were indeed caused by exposure only to the pollens of the local trees.

All of the others, except for two patients allergic to tree, grass and ragweed pollen, suffered from perenially present disorders and were allergic to the four major pollens, namely those of the tree, grass, Plantain and ragweed. They were also allergic to house dust, molds, danders and environmental allergens for some of which treatment is not as yet available.

There were proportionally more of the low dose or the earlier treated patients with symptoms than of those treated with the higher doses or later during the period of administration. But the number of patients reporting symptoms is too small to represent or permit more than a tentative conclusion. In few of the patients did the days of symptoms coincide either with the times of pollen distribution or with the consistent patterns of response as seen in new or untreated patients or in those who, under treatment for other allergens, reported for the first time that the pollen of early Spring had affected them.

In other words, the basic causes of the symptoms of the patients here reported upon are not known, although some were proven to be allergic to an X-factor which will be the subject of a separate report. This allergen

will be added to their injections for 1961, as will other tree pollens of which the extracts were not included in their injections for the tree pollen season of 1960.

It is tentatively concluded that in the treatment of tree pollinosis, according to the method desired, a 2 to 5 per cent failure rate may be expected. But the results of the study point to factors which, when taken into consideration, may lead to more successful treatment.

REFERENCES

1. Brown, E. A.: The treatment of tree pollen sensitivity with single annual injections of emulsified extract, III. Ann. Allergy, 16:353 (July-Aug.) 1958.
2. Brown, E. A.: The results of treatment of Birch, Oak and Elm allergy with single annual injections of emulsified extract, VII. Rev. Allergy & Appl. Immunol., 13:803 (Nov.) 1959.
3. Brown, E. A.: The treatment of pollinosis by means of a single annual injection of emulsified extract, V. Ann. Allergy, 17:34 (Jan.-Feb.) 1959.

*75 Bay State Road*

---

## PROBLEMS OF TOXICOLOGY

We are suddenly realizing that our extensive use of chemicals for all sorts of biological purposes has raised a lot of embarrassing practical problems. Our industrialization depends on burning enormous quantities of fossil fuels resulting in all sorts of air pollution. Our efforts at pest control seriously threaten the balance of nature. Our industrialization and our sewage disposal contaminate our waters. Radiation hazards from nuclear energy efforts bring fear to people everywhere. In an effort to make our food supply go as far as possible, we are adding all kinds of chemicals to our foods, and we are increasing the number of drugs that we use in a terrifying way. Further, we are using an increasing number of potentially toxic chemicals in various industrial processes.

All of these uses constitute public health hazards, in addition to the terrific imbalance wrought in our natural environment. What are we going to do about these matters? Toxicity is suddenly upon us as a social problem.

It is a wholesome indication of the responsibility of scientists concerned that they should meet together to give public expression to their realization of social toxicology, so that free discussion may result in some sort of effective social control.—CHAUNCEY D. LEAKE, Pharmacology Laboratory, The Ohio State University, Columbus, Ohio; Chairman's Remarks, *Proceedings of a Symposium on Problems in Toxicology*, Fed. Proc., 19:1 (Sept.) 1960.

# USE OF ANTIHISTAMINIC AGENTS

S. WILLIAM SIMON, M.D., F.A.C.A.
Dayton, Ohio

FOR THOSE INTERESTED in allergy, enumeration of the uses of antihistamines in the treatment of various allergic conditions would be redundant. It is sufficient to say that the antihistaminic drugs have been used symptomatically for the treatment of the following conditions: allergic rhinitis, aphthous stomatitis, allergic conjunctivitis, atopic dermatitis, contact dermatitis, dermatitis medicamentosa, gastrointestinal allergy, allergic migraine, generalized reactions to insect stings, pruritus ani or vulvi, physical allergy, bronchial asthma in childhood, neurodermatitis, urticaria, angioneurotic edema, eczema, and certain allergic reactions of the eye. In all of these, some relief of symptoms has been reported. Therapeutic use of the antihistamines, while frequently quite effective, is not the preferred method of treatment. In each of these diseases the etiology should be assiduously searched for and, when found, either eliminated as nearly as possible; or if not possible, or only partially so, the usual hyposensitization techniques employed.

During the first ten years of the antihistaminic era, when the number of drugs was expanding rapidly, more and more reasons for their employment were found. We are now in the latter half of the second decade of the antihistamines, and apparently we are seeing a lesser number of reasons for their use. Such use, however, is with better documentation and more effect.

Fewer new antihistaminic drugs are now being introduced; and with few exceptions, we are meeting double or triple drug combinations with added phenylpropanolamine or phenylephrine. Due to the expiration of certain patents on the older and better-known antihistaminic drugs, many pharmaceutical companies have been searching diligently for new drugs which would have a smaller dose, fewer side reactions, and a longer period of action. Unfortunately for them, the search thus far has been rather unrewarding because most of these newer antihistamines are less potent and have just as many side reactions as had the older ones. One advantage that accrues to the medical profession from the expiration of these patents is that it is now possible for certain of the smaller manufacturers to combine two or three well-known and much-used drugs. Combinations of this type at times increase the antihistaminic activity per milligram while in many cases side reactions are reduced or almost eliminated. A great many of these earlier drugs can now be sold over the counter and are being more

Presented as a part of the Instructional Course, The American College of Allergists, Miami Beach, Florida, March 1, 1960.

Dr. Simon is Chief of the Allergy Clinic, Brown General Hospital, Veterans Administration Center, Dayton, Ohio, and Assistant Clinical Professor of Medicine, Ohio State University, Columbus, Ohio.

and more rapidly incorporated into proprietary preparations. If one is to believe television advertising, these combinations, when taken orally, rapidly course through the blood stream, each apparently to its appointed destination, a place which depends, of course, on the complaint of the purchaser. If he has sinusitis, the sinus mucous membrane is immediately shrunken, nasal passages are wide open, and drainage is unhindered. Oh, if it were only thus!

We have even progressed to the place where we are told that by polarizing an antihistamine we can arrive at a dextrorotatory component which has all of the action of the original drug without any of its side reactions.[1]

Now let us consider what we mean by the terms "action" and "side reaction." By "action" is meant the primary anti-allergic functions of shrinkage of swollen mucous membrane, inhibition of thin, watery secretion, and relief of pruritus. In promoting relief, it is assumed that the antihistamine has become attached to the antibody in place of the antigen and thereby has prevented the tissue destruction which results from the combination.[3]

The uses of the antihistaminic drugs for other than treatment of allergic conditions are not so well known but, nevertheless, are exceedingly valuable. In prophylaxis, an attempt is made to prevent the development of adverse symptoms. This was first done by adding a solution of the drug to the pollen used in hyposensitization. Earlier it had been customary, in treating very sensitive individuals, to add a small amount of epinephrine to the injected material. As the antihistaminic drugs were introduced in tablet and capsule form, they were given to the patient usually to be taken half an hour before a pollen treatment and sometimes after treatment, if needed, due to the development of certain undesirable symptoms. When antihistamine solutions became available, they were added to the pollen injection and thereby were absorbed at approximately the same rate as the pollen. Their addition prevented the development of constitutional reactions. Some allergists use these drugs routinely in this way, in all hyposensitizing injections, and apparently obtain as good results as others who never employ them.

From this use of antihistaminic drugs, it was only a step to their prophylactic use to prevent the urticarial and -id reactions of penicillin. Over a period of four years we tried five different antihistamines which were added to each injection of crystalline potassium pencillin G in aqueous solution.[4-8] At this time, a control series of patients who were given the penicillin without antihistamine, produced a reaction rate of about 7 per cent.[4] With sufficient antihistamine added, the reaction rate varied between .24 and .40 per cent.[8] We have never maintained that antihistamines would prevent anaphylactoid reactions, the immediate severe constitutional reaction which follows the injection of a few drops, or possibly even one drop of the penicillin solution because this reaction ensues too fast, and too little antihistamine has been administered and absorbed at this time. It is also not logical to believe that antihistamines added to procaine penicillin would be able to prevent reactions following the slow absorption of this insoluble

drug. We have now used various antihistamines in combination with soluble penicillin in over 10,000 patients and are convinced that the reaction rate can be kept below 0.5 per cent. All antihistamines are not adaptable for this use because certain ones, when mixed with penicillin, form an insoluble gummy precipitate. Among those which may be used are the following: promethazine, diphenhydramine, doxylamine, tripelennamine, pyrilamine, parabromdylamine, methapyrilene, and chlorpheniramine. With those antihistamines whose oral dose is from 25 to 50 milligrams, 5 milligrams of antihistamine are added per hundred thousand units of penicillin; for the antihistamines whose oral dose is below 5 milligrams, 2 milligrams per hundred thousand units of penicillin are added. Most of these can be purchased in multi-dose vials or in ampules and can be used as the diluent for the penicillin. There is also the added advantage that, due to their anesthestic action, there is rarely any residual pain at the site after intramsuclar injection.

Our next experiences with prophylactic antihistamines were in the prevention of allergic reactions to blood transfusion.[9] We take no credit for originality in this; but in a two-year study, which was well controlled, the reaction rate was reduced from 1.7 per cent to .21 per cent. There were approximately 2,000 transfusions with added antihistamine and 2,000 control transfusions. Where the antihistamine was used, only pyrogenic reactions resulted; whereas in the control series the reactions were almost evenly divided between allergic and pyrogenic reactions.

While the transfusion series was being carried on, we were frequently consulted as to how reactions to intravenous urography could be prevented. With some slight success, antihistamines had been tried orally previous to injection of the contrast media.[2] We added chlorpheniramine, the same drug that had been used in the transfusions, to the contrast media in the syringe and reduced allergic reactions from a control rate of 17.3 per cent to 7.1 per cent.[10,11] Practically all reactions except those classified as vasomotor were included such as: nausea, vomiting, urticaria, sneezing, wheezing, and syncope. Even in patients who were unable to take the contrast media due to previous severe constitutional reactions, the injection was made without provoking any type of unusual symptom. Here again, however, a word of caution. If the patient is so sensitive to the contrast media that a drop or two will cause an anaphylactoid reaction, could the minute amount of antihistamine contained in this quantity be expected to prevent it? To 20 or 30 milliliters of the contrast media, 10 milligrams of chlorpheniramine were added. With 20 milligrams, the rate of reaction was reduced even more.

Our latest work with these valuable drugs was to capitalize on their anesthetic properties. It was found that they could be used in place of the various "caine" products for local anesthesia in dentistry.[12] To achieve good results, it was necessary to add a small quantity of epinephrine so that the solution would stay where placed by injection. Nerve blocks were successful as well

as infiltration anesthesia. It is not our intention to substitute antihistamines for the well-tried local anesthetics in use. However, it is felt that in allergic patients, or in others who have had previous though mild reactions to the commonly-used anesthetic agents, it would be easier and safer for the dentist to have a carpule of antihistamine to inject rather than to subject the patient to a general anesthetic or to a possible severe or even fatal reaction from one of the "caine" drugs.

The so-called "side reactions" of the antihistaminic drugs are possibly a misnomer. While these reactions are not the ones originally searched for by the synthesizer, apparently they are almost as frequent percentage-wise as the expected antihistaminic effects. It has often been said that any one of these drugs without side reactions was also low in antihistaminic potency. The most frequent of these reactions has been drowsiness. This has been very useful in hospitalized or bed-ridden patients, particularly those with severe urticaria or extensive dermatitis. However, even in non-atopic patients, many of these drugs have been successfully used as non-habit-forming soporifics or hypnotics.

Another side reaction which may possibly detract in certain patients from the sleep-producing ability, is the drying action on mucous membrane. In those conditions where there is much exudation, this action is very much to be desired; whereas in patients with chronic bronchitis, emphysema, or asthmatic bronchitis, the thickening of the bronchial secretions may cause increased dyspnea and make sputum production much more difficult.

Antihistamines have also been used in patients sensitive to atropine as a mydriatic. This, again, demonstrates the atropine-like action of these drugs.

Although the antihistaminic drugs were at first accepted avidly as treatment for the common cold, this was short-lived. However, with phenylpropanolamine or phenylephrine added to them, they are today being used more for symptomatic relief in colds although it is readily admitted that the course of these infections is in no way shortened.

In conclusion, I have endeavored to cover the myriad uses of these drugs which could, I believe, be called along with the antibiotics, truly "miracle drugs."

## REFERENCES

1. Babcock, George, Jr. and Packard, Louis, A.: d-Chlorpheniramine in allergy. Clin. Med., 6:985 (June) 1959.
2. Getzoff, Paul L.: Use of antihistamine drug prophylaxis against diodrast reactions. J. Urology, 65:1139 (June) 1951.
3. Schulman, P. M. and Fuchs, A. M.: Clinical experiences with β-(p-methylbenzhydryloxy)-ethyl-dimethylamine hydrochloride. Ann. Allergy, 7:502 (July-Aug.) 1949.
4. Simon, S. William: Hypoallergic penicillin. Ann. Allergy, 8:194 (Mar.-Apr.) 1950.
5. Simon, S. William and Feldman, Milton, D.: Hypoallergic penicillin in oil. Arch. Derm. and Syph., 62:314 (Aug.) 1950.
6. Simon, S. William: Hypoallergic penicillin III. (Histadyl-penicillin.) Ann. Allergy, 9:665 (Sept.-Oct.) 1951.

7. Simon, S. William: Hypoallergic penicillin IV. (Chlor-trimeton-penicillin.) Ann. Allergy, 10:187 (Mar.-Apr.) 1952.
8. Simon S. William: Hypoallergic penicillin V. (Pyribenzamine-penicillin). Comparison of results and final conclusions from all studies. Ann. Allergy, 11:218 (Mar.-Apr.) 1953.
9. Simon, S. William and Eckman, William G., Jr.: The use of Chlor-trimeton in the prevention of blood transfusion reactions. Ann. Allergy, 12:182, (Mar.-Apr.) 1954.
10. Simon, S. William, Berman, Henry I. and Barald, Fred C.: Prevention of reactions in intravenous urography (preliminary report). Ohio State M. J., 50:247 (Mar.) 1954.
11. Simon, S. William, Berman, Henry I. and Rosenblum, Saul, A.: Prevention of reactions in intravenous urography. J. Allergy, 25:395 (Sept.) 1954.
12. Simon, S. William, Beard, Alfred B. and Willoughby, Dayton, W.: A safe, effective local anesthetic in dentistry. Mil. Med., 123:377 (Nov.) 1958.

*Brown General Hospital*
*Veterans Administration Center*
*4100 W. Third Street*

---

## METHODS OF SCIENCE

"The strength of science lies in its naivete. Science is like life itself; if we could foresee all the obstacles that lie in our path we would not attack even the first, but would settle down to self-centered contemplation. The average scientist unequipped with the powerful lenses of philosophy, is a nearsighted creature, and cheerfully attacks each difficulty in the hope that it may prove to be the last. He is not given to minute analysis of his own methods. Indeed, if he should become too self-conscious he might lose his power, like the famous centipede who, after too profound analysis of his own method of locomotion, found he could no longer walk. . . .

"I take it that the scientific method, of which so much has been heard, is hardly more than the native method of solving problems, a little clarified from prejudice and a little cultivated by training. A detective with his murder mystery, a chemist seeking the structure of a new compound, use little of the formal and logical modes of reasoning. Through a series of intuitions, surmises, fancies, they stumble upon the right explanation, and have a knack of seizing it when it once comes within reach. I have no patience with attempts to identify science with measurement, which is but one of its tools, or with any definition of the scientist which would exclude a Darwin, a Pasteur or a Kekule."—GILBERT N. LEWIS, *The Anatomy of Science*, Yale University Press.

# REFLEX BRONCHOSPASM CAUSED BY LOCALIZED AIRWAY OBSTRUCTION

## An Asthma-like Syndrome

JOHN L. GUERRANT, M.D. and H. ROWLAND PEARSALL, M.D.
Charlottesville, Virginia

IT IS WELL KNOWN that patients with incomplete obstruction in a major airway may wheeze. Such patients are likely to present unilateral symptoms and signs. They are not expected to suffer generalized wheezing nor respond to symptomatic remedies used for the treatment of asthma. As a rule, there is no evidence for allergy. On the other hand, there are some patients with major airway obstruction who present a syndrome so much like allergic or infectious asthma that the true cause of the symptoms may not be recognized without special studies. This report is concerned with seven such patients seen at the University of Virginia Hospital and one patient seen at the Virginia Mason Hospital. Patients who had readily recognizable airway obstruction at the beginning their illness are not included.

### REPORT OF CASES

*Case 1.*—A fifty-year-old man employed as a cook, was admitted to the University of Virginia Hospital in April, 1955. He had been in good health until one month before admission when he began having attacks of dyspnea and wheezing. There was nothing in his history to suggest allergy or infection. While in the hospital, he had recurrent violent attacks of asthma. The attacks were controlled by epinephrine, intravenous aminophyllin, morphine, and isoproterenol. Between the attacks, he was comfortable, and at such times there were diminished breath sounds over the left lung and inspiratory and expiratory wheezes throughout both lungs. The electrocardiogram, chest x-ray, and chest fluoroscopy showed evidence of left ventricular hypertrophy but no other important abnormality. He was not given a bronchoscopic examination nor did he have skin tests for allergies. On the fifth hospital day, he went into shock and died. Autopsy revealed a bronchiogenic carcinoma arising in the left main bronchus invading locally to involve the lower trachea and adjacent mediastinal structures.

*Case 2.*—A forty-three-year-old woman was first seen in the University of Virginia Allergy Clinic in July, 1952, for lifelong perennial allergic vasomotor rhinitis. She had also had mild wheezing for two months. There were a number of reactions by intradermal tests to dust, feathers, pollen, molds, and foods. Avoidance of important allergens and injections of appropriate allergy extracts led to good control of her symptoms. In December, 1954, she developed a chest cold and began wheezing again. During the next fifteen months, efforts to control her symptoms by intensifying her allergy program, the use of antibiotics, and symptomatic remedies were not very successful. At times, both aminophyllin and epinephrine by injection gave partial

From the Department of Internal Medicine of the University of Virginia School of Medicine, Charlottesville, Virginia, and the Department of Internal Medicine of the Mason Clinic, Seattle, Washington.

relief. For a few weeks, prednisolone gave marked but temporary relief. On a number of occasions, a few wheezes were heard. Two chest x-ray examinations revealed no abnormalities. By March, 1956, she was very dyspneic, and both inspiratory and expiratory wheezing was present throughout both lungs. At that time bronchoscopy demonstrated a tumor in the trachea just below the larynx. Biopsy showed it to be papillary epidermoid carcinoma. A few days later, the larynx, the upper trachea, and the tumor were excised. The tumor extended from the cricoid cartilage to the 5th tracheal ring on the posterior tracheal wall. It was about 1.3 cm. in height. Following the operation, the patient did well. When last seen in May, 1959, she had a permanent tracheostomy and was in excellent health.

*Case 3.*—A forty-four-year-old textile mill worker was first seen in the University of Virginia Hospital Allergy Clinic in March, 1955, because of asthma of five days' duration and a persistent chest cold of six weeks' duration. He reported that his wheezing was worse on the left side. He recognized no allergens that were irritant to him. When he was examined wheezing throughout both sides of the chest was heard. At times, it was more prominent on the left side. There were no important reactions to allergy skin tests. A small amount of pus was washed from the right antrum. He was treated with antibiotics and symptomatic remedies including epinephine, isoproterenol, aminophyllin, ephedrine, and potassium iodide which resulted in temporary but unsatisfactory improvement. After two weeks, x-ray examination showed slight accentuation of the lung markings at the left base and normal chest fluoroscopy. At bronchoscopy, there was hyperemia and edema of the bronchial mucous membrane as well as mucopurulent secretions. At this time, he was treated with penicillin, streptomycin, symptomatic remedies and prednisone. He became more comfortable but continued to have moderately severe asthma requring 10 to 40 mg. of prednisone daily for control. His condition remained unchanged for the next ten months. In February, 1956, he coughed up a sliver of bone, .7 x 2 cm. in size, followed by one ounce of foul sputum. Following this, all his symptoms cleared and when last seen in July, 1956, he was well.

*Case 4.*—A seven-year-old boy developed asthma two and one-half months before being seen at the University of Virginia Hospital in August, 1950. He had developed a mild cough three months before the onset of his asthma. The asthma occurred in episodes of a few hours' duration almost daily with complete relief between attacks. There was nothing in his personal or family history to suggest allergy. Respiratory infections were not common. Physical examination showed inspiratory and expiratory wheezes throughout both lungs. The wheezes were louder on the right side. Intradermal skin tests gave definite reactions to a number of dusts and epidermals and a few minor reactions to foods. A radiograph of the chest showed a metallic foreign body some 5 mm. in diameter in the region of the right main bronchus. At bronchoscopy, the foreign body was seen in the right middle lobe bronchus. The bronchoscopist could not remove it. At thoractomy, a badly damaged right middle lobe was found. It was removed along with the foreign body which proved to be the head of a pencil. The boy recovered. When last heard from, two years later, he was well and free from asthma.

*Case 5.*—A thirty-nine-year-old housewife was in good health until she developed asthma in association with a respiratory infection three years before her first admission. Thereafter she had repeated attacks of severe asthma usually associated with respiratory tract infections. She reported that epinephrine, aminophyllin and antibiotics helped her during the attacks. Between attacks, she was free of wheezing. When admitted to the University of Virginia Hospital in November, 1953, the only

important abnormality on physical examination was depression of the breath sounds in the lower half of the left chest with a few wheezes limited to the same area. A chest radiograph was suggestive of obstructive emphysema in the left lung. A laminogram demonstrated almost complete occlusion of the left main bronchus and partial obstruction of the lower trachea. Chest fluoroscopy showed evidence of air trapping on the left side. There were no important reactions to allergy skin tests. At bronchoscopy, an extensive soft polypoid tumor was seen in the mid trachea. Biopsy showed it to be amyloid tissue. She became progressively worse and died from tracheal obstruction sixty-one days after the first bronchoscopy. Autopsy was not permitted.

*Case 6.*—A fifty-one-year-old laborer had been in good health until six months before admission when he began to cough and wheeze after a very heavy exposure to dust and mold. Three months later, a large thoracic aneurysm was discovered. Symptomatic treatment with prednisolone and other drugs led to considerable improvement. Four days before admission, he stopped taking prednisolone, and his asthma became much worse. He denied unilateral prominence of his wheezing. Except for the fact that dust made him worse, there was no history suggestive of allergy. When first admitted to the University of Virginia Hospital in February, 1957, he was comfortable, but shortly thereafter he developed a violent attack of asthma. At that time, auscultation revealed expiratory wheezing throughout both lungs. During intervals between attacks of asthma, there was marked depression of the breath sounds at the base of the left lung. Shortly after admission, he was started on prednisone. During the first two days in the hospital, the attacks of asthma were controlled by the administration of epinephrine or aminophyllin. Thereafter, asthma was no problem. During a six-week period of hospitalization, several studies were carried out. A chest x-ray demonstrated dilatation of the entire thoracic aorta. Chest fluoroscopy showed that the left lung did not fill on inspiration. Bronchoscopy demonstrated a pulsating bulge into the left side of the lower trachea. On skin tests, there were several weak reactions to common inhalants including dust and molds. At thoractomy, a tremendous aneurysm was found extending from the left subclavian artery to below the diaphragm. It completely compressed the left main bronchus. Attempted resection was not successful, and the patient died. Autopsy was not permitted.

*Case 7.*—A forty-five-year-old farm wife began having asthma attacks ten months before her hospital admission. She noted that house dust and tobacco dust made her worse. She had a family history of allergy. Her local physician found skin reactions to dust and weeds. She improved on treatment with allergy injections and symptomatic remedies. Three months after the onset of her asthma, she developed a crowing sensation in her throat on inspiration and expiration. Six months later, her physician recognized a stridor. At that time, lateral x-rays of the neck demonstrated narrowing of the trachea just below the larynx. Because of this, she was sent to the University of Virginia Hospital, where she was admitted in March of 1956. On physical examination, there were inspiratory and expiratory wheezes over both sides of the chest and over the trachea. The tracheal narrowing just below the larynx was again demonstrated by x-ray. Bronchoscopy was attempted but not successful because of the tracheal stenosis. A tracheostomy was done followed by surgical exploration of the trachea which demonstrated a dense circular stenosis. Biopsy showed only scar tissue. Following this, the trachea was dilated repeatedly. In July, 1956, the tracheostomy tube was removed. The patient became comfortable when the tracheostomy tube was first used and remained so after its removal. In May, 1957, she was still free of respiratory symptoms.

*Case 8.*—A sixty-five-year-old housewife developed a respiratory infection in November, 1956. This was followed by a chronic cough which became worse and also became associated with dyspnea and wheezing. In December, 1956, she was seen in the office where examination failed to demonstrate wheezing. There was nothing in the history to suggest allergy. Chest radiograph gave negative findings. Symptomatic remedies did not help. Because the cough and dyspnea increased, the patient was admitted to the Virginia Mason Hospital on January 26, 1957. While in the hospital, she was observed to have bilateral wheezing during several of her attacks. The chest and sinus radiographs and electrocardiogram showed no abnormalities. A tuberculin test was weakly positive. Allergy skin tests were not done. At bronchoscopy, a 2 x 3 cm. fungating mass was seen just below the opening of the right main bronchus. The lesion appeared to be a carcinoma but sections showed acid-fast organisms. Following the bronchoscopy, the patient was treated with antituberculosis drugs. She had no further wheezing and her cough improved rapidly. It was thought that most of the lesion was removed with the biopsy at the time of the bronchoscopy. When last heard from, eight months later, she had had no recurrence of her symptoms.

## DISCUSSION

These patients with airway obstruction illustrate a number of facts that are of importance to the physician who treats asthma (Tables I, II, III). In them, localized airway obstruction was associated with generalized wheezing. The wheezing was episodic and presented the physical signs of diffuse airway obstruction. Most of them also responded to bronchodilator drugs. Early in their illness, they were thought to have allergic or infectious asthma. Several of them presented features suggestive of this diagnosis. In four, there was evidence suggestive of allergy. In seven, there was no unilateral prominence of symptoms. There was bilateral wheezing in seven, but in five the signs were more prominent on one side. Six responded to bronchodilator drugs. In four, the chest radiograph and in two the chest fluoroscopy showed no abnormalities. On the other hand, such things as absence of infection or allergy, unilateral prominence of symptoms or signs, abnormalities evidenced by chest radiograph or fluoroscopy suggested the presence of a local obstruction. When such a lesion was suspected, it was usually demonstrated by bronchoscopy. In one of the patients with a foreign body, the bronchoscopist did not see the small bone that was present. In the one patient who had no bronchoscopic examination, the lesion could have been seen easily. The lesion involved the trachea or carina in five patients. In three, it was definitely unilateral.

Others have noted that the wheezing of localized airway obstruction may be generalized and easily confused with asthma. Moore[1] reported four patients with carcinoma of the bronchus who were diagnosed and treated as having asthma early in their illness. Two of them were improved after the use of epinephrine. Unger,[2,3] in two articles on asthma, points out that the syndrome may be produced by airway obstruction and mentions a tracheal leiomyoma, a carcinoma involving the carina, and a substernal goiter as specific examples. Holman[4] reported two patients with bilateral wheezing

TABLE I. SYMPTOMS AND PHYSICAL FINDINGS IN PATIENTS WITH REFLEX BRONCHOSPASM AND LOCALIZED AIRWAY OBSTRUCTION

| Case No. | Allergy | Respiratory Infections | Unilateral Prominence of Symptoms | Effect of Bronchodilator Drugs | Unilateral Prominence of Physical Signs | Bilateral Wheezing on Physical Examination |
|---|---|---|---|---|---|---|
| 1 | none | infrequent | no | effective | yes | yes |
| 2 | present | common | no | effective | no | yes |
| 3 | none | infrequent | yes | effective | yes | yes |
| 4 | suggestive evidence | infrequent | no | not determined | yes | yes |
| 5 | none | frequent | no | effective | yes | not heard |
| 6 | suggestive evidence | infrequent | no | effective | yes | yes |
| 7 | present | infrequent | no | effective | no | yes |
| 8 | absent | present | no | not effective | not observed | yes |

associated with an intrabronchial foreign body. He emphasized the difficulty in making a correct diagnosis even when suspected from the history. One of his patients had intermittent wheezing and responded to bronchodilator drugs. Greer and Winn[5] reported a patient with a leiomyoma of the trachea which masqueraded as asthma for three years. This patient improved when treated with epinephrine, potassium iodide, ACTH and other symptomatic remedies. Swineford[6] lists bronchial obstruction as one of the causes of wheezing in his report on the classification of the causes of asthma.

It is likely that the localized lesion in these patients served as an irritant, setting off generalized bronchospasm. This is supported by the fact that most of these patients were improved by drugs that ordinarily relieve bronchospasm. The mechanism for such a process is present. The human bronchial mucous membrane is well supplied with afferent nerve endings arising from the vagus. They are thought to have a tactile function.[7] Mechanical stimulation of the mucous membrane of the trachea or large bronchi in dogs and rabbits causes a reflex cough.[8] Electrical stimulation of the isolated vagus nerve in dogs and cats results in narrowing of the trachea and narrowing and shortening of the bronchi. Stimulation of one vagus affects the bronchi of both lungs.[9] It is a common observation among bronchoscopists that the introduction of a bronchoscope into the tracheobronchial tree of patients with asthma is likely to precipitate an acute attack of wheezing. In dogs, bronchial constriction is produced by pulmonary embolism.[10] It is prevented by bilateral vagal section or large doses of atropine.[10,11] There is no completely satisfactory explanation for the fact that a localized lesion seems to set off generalized bronchospasm in only an occasional patient. Neither is there an explanation for the fact that only some of the patients who have respiratory allergy or respiratory infection wheeze. Such patients may have some fundamental abnormality of the bronchial neuromuscular system that makes it more irritable.

There is an entirely different mechanism that may be of importance in producing intermittent wheezing in our patients. Dekker and Groen[12] have suggested that compression of the larger air passages by the high intra-

TABLE II. CHEST X-RAY, FLUOROSCOPY, AND BRONCHOSCOPY IN PATIENTS WITH REFLEX BRONCHOSPASM AND LOCALIZED AIRWAY OBSTRUCTION

| Case No. | Chest X-Ray | Fluoroscopy | Bronchoscopy |
|---|---|---|---|
| 1 | lungs normal | lungs normal | not done |
| 2 | lungs normal | not done | tracheal tumor seen |
| 3 | lungs normal | lungs normal | generalized bronchial inflammation |
| 4 | metallic foreign body | not done | foreign body seen in RML bronchus |
| 5 | unilateral obstructive emphysema. Narrowing of left main bronchus and lower trachea | air trapping on left side | tracheal tumor |
| 6 | aneurysm of thoracic aorta | poor filling of left lung | compression of lower trachea |
| 7 | lateral x-ray of neck demonstrated tracheal narrowing | not done | tracheal stenosis |
| 8 | lungs normal | not done | mass in right main bronchus |

thoracic expiratory pressure that asthmatic patients produce is an important factor in producing the expiratory wheezing that is so characteristic of asthma. They demonstrate by special radiographs of the trachea, by bronchoscopy, and by *in vitro* experiments on an excised human trachea and lungs that such compression can occur. Individuals with incomplete obstruction in the larger airways would be particularly susceptible to increased expiratory obstruction from this mechanism when they try to increase their expiratory rate.

## SUMMARY

Eight patients with organic obstruction in a major airway are described. At some time during the course of their illness, they had either asthma or a syndrome easily confused with asthma. All had episodes of wheezing. Some presented evidence of allergy, bilateral asthmatic râles, a response to bronchodilator drugs, or normal chest as revealed by x-ray examination. In one case, bronchoscopy did not reveal the obstruction. Careful observation of the patient who wheezes and coughs will usually demonstrate one or more leads pointing to the correct diagnosis of localized airway obstruction. These include absence of allergy, unilateral prominence of symptoms or signs, abnormal chest, unequal filling of the lungs on fluoroscopy,

TABLE III. CAUSE AND LOCATION OF LESION AND RESULTS OF TREATMENT IN PATIENTS WITH REFLEX BRONCHOSPASM AND LOCALIZED AIRWAY OBSTRUCTION

| Case No. | Nature of Lesion | Location | Treatment | Results |
|---|---|---|---|---|
| 1 | bronchiogenic carcinoma | left main bronchus and lower trachea | symptomatic | died |
| 2 | carcinoma | trachea | excised | well |
| 3 | foreign body (bone) | not determined | symptomatic | well |
| 4 | foreign body (metallic) | RML bronchus | lobectomy | well |
| 5 | primary amyloidosis | trachea | attempted removal through bronchoscope | died |
| 6 | aneurysm of aorta | trachea and left main bronchus | attempted resection | died |
| 7 | fibrosis | trachea | dilated | well |
| 8 | tuberculosis | right main bronchus | antituberculosis drugs | asthma cleared |

and cough out of proportion to the severity of the illness. When such a lesion is suspected, it can usually be demonstrated by bronchoscopy. Localized airway obstruction may be present in patients who respond to symptomatic treatment.

The cause of the obstruction in these patients was carcinoma of the trachea or bronchus, a foreign body in two cases, primary amyloidosis of the trachea, tuberculosis of the bronchus, fibrosis of the trachea, and aneurysm of the thoracic aorta.

REFERENCES

1. Moore, M. W.: Carcinoma of the lung with asthmatic symptoms. Ann. Allergy, 3:271 (July-Aug.) 1945.
2. Unger, L.: The recognition of nonallergic asthma. Dis. Chest., 22:671 (Dec.) 1952.
3. Unger, L.: Chronic bronchial asthma in the older age group. M. Clin. North America, 40:115 (Jan.) 1956.
4. Holman, J.: The asthmatic syndrome precipitated by foreign bodies in the lung. J. Allergy, 28:182 (Mar.) 1957.
5. Greer, A. E. and Winn, G. L.: Leiomyoma of trachea. J. Thor. Surg., 33:237 (Feb.) 1957.
6. Swineford, O., Jr.: Asthma: Classification of causes. J. Allergy, 25:151 (Mar.) 1954.
7. Larsell, O. and Dow, R. S.: The innervation of the human lung. Am. J. Anat., 52:125 (Jan.) 1933.
8. Larsell, O. and Burget, G. E.: The effects of mechanical and chemical stimulation of the tracheobronchial mucous membrane. Am. J. Physiol., 70:311 (Oct.) 1924.
9. Francis, B. F.: Changes in the shape and size of the tracheobronchial tree following stimulation of the vagosympathetic nerve. AMA Arch. Surg., 19:1577 (Dec.) 1929.
10. Jesser, J. H. and DeTakats, G.: The bronchial factor in pulmonary embolism Surgery, 12:541 (Oct.) 1942.
11. Boyer, N. H. and Curry, J. J.: Bronchospasm associated with pulmonary embolism. AMA Arch. Int. Med., 73:403 (May) 1944.
12. Dekker, E. and Groen, J.: Asthmatic wheezing. Compression of the trachea and major bronchi as a cause. Lancet, 1:1064 (May 25) 1957.

*Department of Internal Medicine (Dr. Guerrant)*
*University of Virginia Hospital*

## TAKE CARE TO GET INFORMATION

We live by information, not by sight. We exist by faith in others. The ear is the area-gate of truth, but the front door of lies. The truth is generally seen, rarely heard; seldom she comes in elemental purity, especially from afar; there is always some admixture of the moods of those through whom she has passed. The passions tinge her with their colours wherever they touch her, sometimes favourably, sometimes the reverse. She always brings out the disposition, therefore receive her with caution from him that praises, with more caution from him that blames. Pay attention to the intention of the speaker; you should know beforehand on what footing he comes. Let reflection assay falsity and exaggeration.—BALTHASAR GRACIAN (From *The Art of Worldly Wisdom* translated by Joseph Jacobs, Macmillan & Co., London, 1927.)

# SUBCUTANEOUS REACTION OF RABBITS TO HORSE SERUM

**Historical Document**

J. H. MASON KNOX, Ph.D., M.D., W. L. MOSS, M.D.,
and
G. L. BROWN, M.D.

Baltimore, Maryland

THE OBJECT of the following study is to determine the effect of subcutaneous injections of horse serum upon rabbits in order to ascertain whether this procedure can be used as a test of altered reactivity (allergy) or of acquired anaphylaxis. Heretofore, most of the experimentation upon anaphylaxis has usually resulted in the death of the animal. Rabbits are known to be less susceptible than guinea pigs to foreign sera, and it was considered possible that local, but quite as definite, phenomena might be obtained in rabbits after repeated inoculations of small quantities of horse serum.

*Previous Work.*—But few investigators have been interested in this particular inquiry. Arthus[1] in 1903, following the ideas of Richet, first noted the effect of injections of horse serum upon rabbits. He found that the first injections produced no clinical consequences, but that after later injections intense local swellings were produced, and at times definite necrosis. In a few instances, sudden death of the animal followed. This result was more frequent after intraperitoneal and intravenous injections. Later von Pirquet and Schick[2] injected rabbits subcutaneously in the ear and produced edema after the second injection, using rather large amounts of serum, one to three cubic centimeters. Whereas Arthus had considered that this production of local reaction depended on the number of previous injections, von Pirquet and Schick showed that the interval between the first and second injections was the more important factor, and that the local swelling followed even after the second injection, provided that about ten days elapsed between the first and second inoculations. These writers found also that horse serum was specific in its action, that a previous injection of horse serum did not affect subsequent injections of other sera, and that no reaction followed the inoculation of horse serum in animals that had been previously injected with other sera. They found also that animals in which horse serum had been previously injected reacted locally after the injection of rabbit serum from an allergic rabbit.

---

From the Laboratories of the Pediatrics Department and of the Johns Hopkins Hospital.

Reprinted from the *Journal of Experimental Medicine*, New York, 12:562-573, 1910, with permission of the authors and publishers.

In the interests of space, the tables referred to are omitted since their significance is clear from the text to present day readers.

Later Nicolle[3] produced a local edema in rabbits which had previously received a large amount of serum from an allergic rabbit, by injecting it subsequently with horse serum. Since 1907 nearly all authors have been interested chiefly in the general phenomena of anaphylaxis, and have paid but little attention to the local reaction, and, moreover, most of the work has been done with guinea pigs and not with rabbits. In regard to local reaction on guinea pigs, the observation of Paul Lewis must be mentioned. He showed that in pigs which survived the allergic shock, large areas of edema were often produced.

*Description of Test.*—In our first experiments twenty rabbits, ten males and ten females, of nearly equal weight, were selected. Two (Nos. 48 and 37) were reserved as controls.

The remaining eighteen rabbits were inoculated in an ear vein with varying amounts of sera as follows: Nos. 55 and 53, 0.1 cubic centimeter of horse serum; Nos. 51 and 27, 0.1 cubic centimeter of serum and 9.9 cubic centimeters of normal salt solution; Nos. 26 and 78, 0.5 cubic centimeter of serum; Nos. 42 and 71, 0.5 cubic centimeter of serum and 9.5 cubic centimeters of salt solution; Nos. 56 and 30, 1 cubic centimeter of serum; Nos. 4 and 49, 1 cubic centimeter of serum and 9 cubic centimeters of salt solution; Nos. 14 and 35, 5 cubic centimeters of serum; Nos. 34 and 40, 5 cubic centimeters of serum and 5 cubic centimeters of salt solution; Nos. 50 and 10 with 10 cubic centimeters of serum each.

On the sixth day after the intravenous injections, one rabbit from each group, ten in all, were inoculated subcutaneously in the ear with 0.1 cubic centimeter of a 10 per cent solution of horse serum. This produced no local reaction in any of the rabbits. The same ten rabbits were injected with the same amounts of serum every other day for three days. After the third injection, most of the rabbits, as indicated in the table, showed a positive reaction, definite swelling, and redness of the ear at the point of inoculation. The difficulty of inoculating the serum into the scanty subcutaneous tissue of the ear without injury was recognized. It was thought that some of the redness and swelling might be due to mechanical injury, and after the twelfth day of the injection, the tests were made into the carefully shaved skin of the abdomen. Local reactions began to appear ten days after the original intravenous injection of serum, and continued, with some exceptions as long as the animals were tested; that is, the hyper-susceptibility to horse serum developed in the rabbits remained for at least two months and a half. The first test of the second rabbits of each of the ten groups was made on the fourteenth day after the original intravenous injection and consisted in the injection of 0.1 cubic centimeter of a 10 per cent solution of horse serum into the skin of the abdomen. These second numbers of each group seemed to average about the same number of definite reactions as those which had been

injected several times previously. It was, therefore, concluded that the hyper-susceptibility to the serum was the result of the first intravenous injections, and that this hyper-susceptibility developed in most of the rabbits in from ten to fourteen days.

Several interesting individual variations are to be noted. Rabbit No. 48, a control animal, which had received no serum originally, exhibited a suggestive reaction on the third and fifth day after the first subcutaneous injection, and remained definitely positive from the ninth day after this injection. Apparently this animal was unusually susceptible to horse serum and developed its anaphylaxis because of the subcutaneous injection of 0.1 cubic centimeter of a 10 per cent solution of horse serum. Another rabbit, No. 71, showed a complete insusceptibility to horse serum during two months and a half of observation. After the sixteenth day, 0.1 cubic centimeter of undiluted horse serum was used in making the intradermal tests. In general, the reactions seemed a little more constant in those animals that had originally received the larger amounts of serum, though there were exceptions to this observation. On the fifty-sixth day, 0.05 cubic centimeter of horse serum was used intradermally in making the tests. The animals seemed just as susceptible to this smaller amount of serum.

In making the tests it was always endeavored to insert the point of a small hypodermic needle into and not under the skin, and to produce by the injection a small translucent bleb.

To verify these results, a second series of animals, four in number, were each injected intravenously (ear vein) with 5 cubic centimeters of horse serum. On the sixth day they were tested by an intradermal abdominal injection of 0.1 cubic centimeter of horse serum. None of them reacted. This test was repeated on the fourteenth and sixteenth days with negative results. After a similar test on the nineteenth day, three of the animals reacted positively, but the fourth was not definitely positive until the twenty-seventh day, and was negative to three subsequent tests but remained constantly positive after the thirty-eighth day. Rabbit No. 48 of the first series, already shown to be susceptible to horse serum, was again injected with this second series as comparison. A sixth rabbit, No. 2, which had received 1 cubic centimeter of horse serum subcutaneously, reacted positively on the thirteenth day to the intradermal injections of 0.1 cubic centimeter of horse serum.

In order to determine whether even smaller intradermal injections of horse serum could not be used to determine the presence of anaphylaxis in rabbits, a third series of rabbits, twelve in number, was carried on. Of these, two were used as controls, and the others, in groups of two, were injected intravenously with horse serum as follows: first group controls; second group, 0.1 cubic centimeter; third group, 0.5 cubic centimeter; fourth group, 1 cubic centimeter; fifth group, 2.5 cubic centi-

meters; sixth group, 5 cubic centimeters. On the sixth day one animal of each of these groups was injected with 0.01 cubic centimeter of horse serum intradermally. The rabbits, in Groups 5 and 6, which had received the largest amounts of serum intravenously, showed definite local reaction on the seventh day. The susceptibility in these animals remained fairly constant after all subsequent injections.

On the twelfth day, all the animals were injected with 0.01 of 1 cubic centimeter of horse serum intradermally. Those receiving the test for the first time reacted nearly as readily as the other members of their group which had been tested several times before. This series, therefore, confirms the observation of Series 1 and 2 and adds the additional fact that a very small amount of horse serum is sufficient to produce a local skin reaction in a susceptible animal. A thirteenth rabbit, No. 59, was injected with 1 cubic centimeter of rabbit serum and tested on the seventh and fourteenth days with an intradermal injection of 0.01 cubic centimeter of rabbit serum with negative results.

*Phenomena.*—The local changes at or near the point of inoculation described as a reaction varied considerably at different times and in different animals. A typical reaction to horse serum in a sensitive rabbit may be described as follows: the bleb produced by the intradermal injection of the serum disappears in a short time, and no change is noticed at the seat of injection for ten to twelve hours. After this time the skin may become a little reddened and infiltrated, so that when it is taken up between the fingers in a fold, it seems definitely thickened as compared with a fold of skin elsewhere. The swelling and redness continue to increase and reach their height in about twenty-four hours, when there may be a definitely raised, brawny mass, perhaps one or two centimeters in diameter. The skin of the reacting area is red and increased in temperature, and the mass is definitely tender. Reactions which were less severe exhibited only a more or less diffuse infiltration of the skin at the point of inoculation with little or no redness or heat in the shaved area compared to that of the rest of the skin. In a number of rabbits the reaction was much more marked. In these the infiltration began sooner, the part affected extending five to ten centimeters, became very tense, swollen and red, and on several occasions partly necrotic. Reactions of this fulminating character often lasted for two or three weeks, whereas those which produced less severe changes diminished after twenty-four hours. On several occasions the reactions took the form of an unusually firm, sharply circumscribed round mass with less increase in local temperature and redness than was usually the case. It was thought at one time that these firm nodules were the result of a skin test following closely the injection of a large amount (ten cubic centimeters) of horse serum intraperitoneally. We were unable, however, to reproduce later

this form of reaction, and do not know to what factors it was due. So far as we could determine there was little constitutional disturbance during the time of reaction. The rabbits seemed lively and ate well. On several occasions following the injection of large amounts of serum intraperitoneally the rabbit appeared shocked. One had a short convulsive seizure followed by the passage of bloody urine. All these quickly and completely recovered. In the whole number of more than forty rabbits injected, no fatalities occurred.

*Microscopic Appearances.*—A typical swollen reacting area was excised for microscopic examination and may be described as follows:

The epidermis is everywhere intact and presents no abnormalities. Immediately beneath the epidermis the tissues were slightly infiltrated, but there is little if any accumulation of small round cells. Throughout the rest of the section of the skin and extending to the muscle layer, the tissues are definitely edematous, the fibrous strands being somewhat separated and compressed. In this area there is a marked increase in the number of leucocytes, many of them scattered, but the greater number gathered in small interstitial groups about the blood vessels. These cells about the vessels consisted mainly of polymorphonuclear leucocytes. The vessels are everywhere moderately injected and filled with red blood corpuscles. There is little if any evidence of marked hemorrhage, although some extravasation of red cells is noted about the smaller vessels. The muscle layer beneath the skin is unchanged. The whole appearance of this section suggested a moderately acute infiltration and inflammation.

*Precipitine Test.*—The serum of the rabbits was tested at intervals with horse serum for the presence of precipitines. The microscopic method was used for the most part, the results being controlled several times by microscopic test. The method used had been employed formerly by Dr. von Pirquet in agglutination of streptococci[4] and is briefly as follows:

On a cover slip three minute drops of horse serum, one undiluted, one diluted 1 to 10, and the third, 1 to 100, are placed in a row with a sterile platinum loop. Immediately opposite each drop of the horse serum is placed a drop of the same size of rabbit serum and the opposing sera are mixed gently together. The cover slip is now inverted over a hollow slide and placed in the incubator for three hours or for a longer time in room temperature, when under the microscope the precipitate is examined. When the precipitate forms, it is observed as a more or less extensive granular cloud. It will be noted that the precipitines were present in the blood of nearly all animals exhibiting local reaction, and were occasionally present where local reaction was not obtained. The dilution of the horse serum made but little difference in the intensity of the reaction.

*Anti-anaphylaxis.*—Having shown that the anaphylaxis, or the heightened susceptibility to a foreign serum could be demonstrated by a skin reaction, it was interesting to determine whether a lowered state of susceptibility, or the so-called anti-anaphylaxis, could be proved in the same way. Nicolle first showed that experimental animals injected during incubation time not only were not killed by a second injection, but that their hyper-susceptibility was definitely lessened during this period. Besredka[5] and Rosenau and Anderson[6] working with guinea pigs found that when these animals survived a test injection they did not show general phenomena of inoculation again in twenty-four hours. In tuberculosis, also, it has been proven that after large doses of tuberculin subcutaneously, the reaction of the skin to vaccination with tuberculin (the von Pirquet test) disappears. A kind of tuberculin immunity develops. In our experiments we were unable to decrease the susceptibility of our rabbits to the intradermal injections of horse serum. Repeatedly sensitized animals which were exhibiting definite local reactions to every injection of horse serum were given large doses, five or ten cubic centimeters, intravenously or intraperitoneally, but an intradermal injection made within twenty-four hours always produced a definite local reaction. In several instances after a procedure of this kind, the localized swelling was usually hard and circumscribed, but this form of reaction could not be regularly obtained.

*Transmission of Susceptibility to Offspring.*—A number of experiments were carried on to determine whether it was possible to transmit this susceptibility, which is developed in rabbits, and indicated by the local skin reaction, to their young. Anderson[7] had shown that the toxic hypersusceptibility to horse serum, as indicated by the general phenomena of anaphylaxis and ending in death, can be transmitted in guinea pigs from a sensitized mother to her young. In several experiments the injection of horse serum into the offspring of such sensitized mothers was fatal in less than an hour, while much larger quantities of horse serum produced no effect upon young guinea pigs from unsensitized mothers. Two litters of rabbits, one six in number and three weeks old, from the offspring of a highly sensitized mother which had markedly reacted just before the birth of her young, were inoculated with 0.02 cubic centimeters of horse serum every other day intradermally into the abdomen, and on the fifth day following developed a definite but slight thickening and infiltration of the skin a few hours after the injection. At the same time a litter of five rabbits from an unsensitized mother were similarly injected and reacted positively in just the same period of time, but more vigorously than did those of the first litter. The reactions following the last injections in the second series were all accompanied by marked induration and considerable hemorrhage. Our results suggest, therefore that the susceptibility of the sensitized rabbit, as indicated by the skin reaction, is not

freely transmitted to its offspring. A comparison of the effects upon the young of these two litters would suggest, however, the possibility that the offspring of the sensitized rabbit have acquired some allergy to horse serum, that is, the property of an accelerated formation of ergines.

*Leucocytic Count.*—It was thought that it would be of interest to determine whether the leucocytes underwent any change either in their total number or differential count following the sensitizing injection of serum or following the skin reaction induced by the subsequent intradermal injection of minimal doses of serum. To determine these points four fresh rabbits of approximately the same age and weight were selected, and before any injections were given, leucocyte counts were made as follows: at nine a.m., one p.m., and five p.m., on the first day, and at nine a.m. on each of the three successive days. After a rest of about a week, a similar series of counts were made. Another week was allowed to elapse and then sensitizing injections of serum were made intravenously. The first rabbit was given 0.1 cubic centimeter, the second, 2.5 cubic centimeters, and the third, 5 cubic centimeters, while the fourth was not injected and served as a control. The leucocytes were then counted exactly as on the two preceding occasions. After a lapse of fourteen days all four rabbits received intradermal injections of 0.01 cubic centimeters horse serum and a fourth series of counts was carried out. The total number of leucocytes and differential counts were made on each occasion, in all twenty-four total leucocytes and twenty-four differential counts on each rabbit.

The leucocytes varied through wide limits both in their total number and in the differential counts, the variations being just as great in the two series of counts made before any serum had been injected as in those series following the sensitizing injection and the subsequent test injection, and no relation could be made out between the injections and the leucocyte curves.

The detailed results of these counts are too long to include here. They will be reported in a separate paper.

## CONCLUSIONS

1. Anaphylaxis or allergy of rabbits against horse serum can be proved by subcutaneous test.

2. The test is best made in the following way. The skin of the animal, preferably of the abdomen or flank, is shaved. (This should be done a few hours before the injection.) The injection is made by means of a small hypodermic syringe and intradermally. An effort was made not to inject the serum under the skin. Those injections were considered most favorable by which the serum remained as a small bleb in the skin

proper. Undiluted horse serum was used for most of the experiments. The amount injected varied from 0.01 cubic centimeter to 1 cubic centimeter. The reaction seemed as definite after 0.01 cubic centimeter as after a larger quantity.

3. The specific reaction appears in from twelve to twenty-four hours after the test is made and it reaches its maximum in from twenty-four to thirty-six hours. It consists of a local swelling extending from .05 to 2 centimeters from the point of inoculation. The skin involved in the raised area is usually red and hotter than the surrounding skin. Macroscopically and microscopically the reacting area has the appearance of a local acute inflammation.

4. The altered reactivity (allergy) or hyper-susceptibility (anaphylaxis) sets in usually in from ten to fifteen days after the first injection of horse serum, and lasts at least three months. Individual rabbits show marked variation from the average time of the development of anaphylaxis.

5. The appearance of precipitines against horse serum in the blood of rabbits appears nearly synchronously with the allergic condition.

6. After large injections of serum the allergic rabbits still react subcutaneously. A suppression of allergy which would correspond to the so-called anti-anaphylaxis could not be proved.

7. Also in regard to the offspring of injected rabbits the subcutaneous test was not positive. The young of these rabbits did not develop a more active allergy than the young of normal rabbits.

8. Neither the injection of considerable quantities of horse serum nor the development of a marked local reaction in the skin after intradermal inoculations of horse serum in a sensitized rabbit is accompanied or followed by greater variations in the number or types of leucocytes in the circulating blood than is found in control animals.

It is a pleasure to acknowledge our indebtedness for much help to Professor von Pirquet, at whose suggestion the work was undertaken.

---

**FIRST PRINCIPLES**

Whoever hestitates to utter that which he thinks the highest truth, lest it be too much in advance of the time, may reassure himself by looking at his acts from an impersonal point of view. . . . It is not for nothing that he has in him the sympathies with some principles and repugnance to others. He, with all his capacities, and aspirations, and beliefs, is not an accident, but a product of the time. He must remember that while he is a descendant of the past, he is a parent of the future, and that his thoughts are as children born to him, which he may not carelessly let by.—HERBERT SPENCER (1820-1903)

# Editorial

*The opinions expressed by the writers of editorials in the* ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

## BACTERIAL ALLERGY

Many substances of bacterial origin are able to produce specific sensitization in man and in animals. The question has been asked whether sensitization to bacterial materials could be a causative agent in allergic disease. That this indeed be the case, has been asserted in nearly every textbook concerning allergic affections. A library could be filled with papers and monographs supporting the thesis and the diagnostic and therapeutic procedures based on it. Few of us will deny the likelihood that the thesis has merit. However, the first condition for progress in scientific questions is the distinction between hypothesis and facts supported by solid evidence. Thus, it may be worthwhile to consider briefly how firm is the ground upon which the edifice of our beliefs is built.

We stand on firm ground when we can reproduce the allergic manifestations in the patient by means of the antigen incriminated. This has hardly ever been achieved with antigens of microbial origin except in the cases of massive occupational exposure in biological laboratories.

On the other hand, evidence that a substance has sensitizing ability is no proof that such sensitization can produce clinical disease. Even if it can be shown that a given person is specifically reactive to a given agent, this specific reactivity is not necessarily proof that the particular agent is the cause for the person's allergic complaint. This would hardly need stating were it not for the peculiar circumstance that these homely verities are so often forgotten when sensitization by bacterial antigens is argued.

In order to stay within manageable limits, it will be necessary to restrict this discussion to those affections which are foremost in the allergists' minds when they speak of bacterial allergy, namely those of the respiratory tract. The mouth, the nose and the pharynx are inhabited by micro-organisms in large numbers and seemingly unlimited variety. For the physician, these micro-organisms fall into two categories: those capable of producing infection (on which the physician is briefed in considerable detail) and those lacking this ability and therefore summarily dismissed from consideration as saprophytes.

The pathogens frequently leave their mark on the host by specific sensitization which can be demonstrated in the form of dermal reactions and other tests with vaccines or fractionation products of the microbial body. To what extent such sensitization modifies the course of infection

is beyond the scope of this discussion. The problem at hand must also be separated distinctly from that of the (non-specific) influence of infection upon allergic reactivity. What concerns us at this moment is whether previous contact with a pathogenic micro-organism in the form of infection can leave the host in a state where he would on future contact react with the signs of allergic disease—in our case with allergic coryza or asthma. This writer knows of no definite evidence which would permit a statement with any degree of assurance. A critical examination of this problem certainly would be of great interest and should not be out of the range of the possible.

However, the problem does not rest with the role of the pathogens. It is the saprophytic micro-organisms that present the great bulk of the flora on the upper respiratory tract. Moreover, they are there all the time and not only sporadically as is the usual case with a pathogen. Thus, non-pathogenic bacteria would seem to be the likely prime suspects for a role in allergic disease. The lack of known reactivity in the host should not distract us. After all, one of the fundamental aspects of allergic disease is the subject's violent immunological response to an agent that is indifferent to the population at large.

The saprophytic flora of the human oral and nasal cavities has been of interest only to a few microbiologists, often those connected with dental schools. The information presently available cannot compare with that concerning the relatively few pathogenic micro-organisms. One can say without exaggeration that no individual's nose and pharynx have ever been exhaustively catalogued for their flora. There is much more than is revealed by the routine of culturing in a laboratory, which is tailored to provide information on the presence of pathogens. A complete inventory would have to include the culture and identification of many forms—both aerobic and anaerobic ones—some of which have never been studied in detail. In order to be of value to the allergist, the investigation would have to be extended to the immunological properties of these micro-organisms. Furthermore, information would have to be obtained on the fluctuations of this flora. A correlation between the presence of a suspected micro-organism and clinical symptoms and conversely the disappearance of symptoms with the disappearance of the micro-organisms would be an essential part of the evidence to be gathered. Once data of this kind become available, clinical investigation would obtain the tools with which to proceed further.

This sounds like a large order, and it is. But it could be done if the facilities would be made available to properly prepared and patient investigators.

Experience has shown that in each category of allergically active substances only a few eventually turn out to be important either for reasons of prevalence or of special endowment with antigenic activity. Thus it may perhaps not be over-optimistic to expect that in the case of allergy

to bacteria, the number of species of practical interest would stay within manageable limits.

One thing is sure. No one can complain that there is a dearth of fundamental problems to be explored in our specialty.

—A.J.W.

## SMOKING AS A HEALTH PROBLEM

Chronic smoking has been shown to increase the frequency of pulmonary cancer, its detrimental effect on the circulatory system is definite, etc. The most notable detrimental effect on health of chronic smoking is, however, the chronic bronchitis and bronchiolitis caused by it: When a chronic bronchiolar process has led to the obstruction of the bronchiolar lumen, the person concerned inevitably develops obstructive pulmonary emphysema. The process is so slow, often taking twenty to thirty years, that the layman can easily fail to discern the causal relationship between smoking and the emphysema. An investigation has recently been conducted in Finland on the relationship of chronic smoking to obstructive pulmonary emphysema in a larger population group than ever before. It was made possible by a new, simple device developed for the demonstration of bronchiolar obstruction. The results of this study covering 3,375 persons aged over fifteen (75 per cent of the population of over fifteen in the rural commune studies) were as follows: of 137 men with pulmonary emphysema, 56 per cent were heavy smokers (had smoked 10 g or more of tobacco per day for a minimum of ten years). In the group of men with healthy lungs, the corresponding percentage was only 33.4. The frequency of pulmonary emphysema among males was 0.5 per cent for non-smokers and 1.8 per cent for heavy smokers in the fifteen to thirty-nine year old group. The difference was thus fairly small. On the other hand, in the group of men aged forty to sixty, the difference was great; 4.9 per cent of the non-smoker and 16.7 per cent of the heavy smoker group had emphysema. The difference was highly significant. The difference was equally clear in the group of men over sixty, the corresponding percentages being twenty-three in the non-smoker and forty in the heavy smoker group. As far as women are concerned, a statistical analysis of the relationship between heavy smoking and pulmonary emphysema was impossible since only 0.6 per cent of them belong to the heavy smoker group. It is notable that the pulmonary emphysema frequency of non-smoker men and women was practically the same in the different age groups. It would thus seem that pulmonary emphysema has become a male disease only because smoking is commoner among men. Although chronic smoking ostensibly causes no other direct inconvenience than smoker's cough, which the smoker usually ignores completely, every chain smoker must consider that when middle-aged the certainty that he will have an invalidating pulmonary emphysema is twice as great for him as for his non-smoking neighbor.—Excerpt from "Smoking as a Problem Affecting Health," by Dr. Klaus A. J. Jarvinen, Helsinki, Finland. World M. J., 7:302 (Sept.) 1960.

# Progress in Allergy

## PEDIATRIC ALLERGY

### A Critical Review of the Literature

SHELDON C. SIEGEL, M.D., F.A.C.A. and
BAILEY J. LOVIN, JR., M.D.
Los Angeles, California

THE PRESENT REVIEW of pediatric allergic literature covers that period from the last similar review, which included articles from 1955 to the later part of 1957, through 1959.[1] Since pediatric allergy encompasses almost all of allergy, articles relating to pediatric allergy and, in some instances, papers dealing mainly with adults, will be included in the review. However, special emphasis will be placed on those articles which were published in the pediatric literature and those concerned with the problems relating to pediatric allergy. In a review of this nature and scope, it is obvious that all papers published on subjects that might be of interest to the pediatrician and the pediatric allergist could not be included. For more comprehensive information on these different aspects of allergy—dermatology, immunology, microbial allergy, enzymology, pollinosis, bronchial asthma, etc., the reader is referred to the many excellent reviews that have appeared in the past two years.[2-13]

Since the last review on pediatric allergy appeared, very few major advances or changes have been made in the diagnosis and management of allergic diseases, and our knowledge of basic underlying mechanisms of the diseases of hypersensitivity remains fragmentary. In the area of symptomatic therapy, there has been the remarkable development of the newer synthesized steroids, the re-introduction of the repository method of treating pollinosis, the advocation of penicillinase as a new method for treating penicillin reactions, and the introduction of griseofulvin for the oral treatment of certain fungus infections. Our concepts of the hypersensitivity reaction have also been broadened to include several different mediating substances, as well as soluble antigen-antibody complexes. Inborn errors of metabolism have also been shown to play a role in hemolytic reactions to certain drugs and in favism. Auto-immune mechanisms have been clearly demonstrated to be involved in such diseases as thyroiditis. Although new immunologic research tools have been developed, they as yet have not been generally applicable to clinical practice. These latter advances will only be briefly alluded to in the review. The main body of the paper will be devoted to the clinical phases of allergy.

To maintain some continuity with the previous reviews, the format used by the previous authors will be maintained with some minor modifications.

From the Children's Medical Group, Los Angeles, California.
Dr. Siegel is Clinical Associate Professor of Pediatrics, University of California, Los Angeles.

## ATOPIC DERMATITIS

The number of divergent opinions as to the pathogenesis and appropriate therapy of atopic dermatitis attests to our lack of understanding of the etiology of this disease, as well as to the difficulties that can be encountered in its management. Nevertheless, a number of patho-physiologic studies in patients with atopic dermatitis have appeared which begin to shed some light on this problem.

Strauss and Kligman[14] have recently reviewed some of the current concepts concerning the etiology of atopic dermatitis. These authors indicated that there are three possible etiologic relationships between atopic dermatitis and the atopic state: First, atopic dermatitis is a specific cutaneous manifestation of an allergic reaction; secondly, there is no specific etiologic relationship between atopy and atopic dermatitis; and finally, there is a mechanism by which specific allergens can provoke exacerbations of an existing etiologically unrelated dermatitis in a susceptible individual. Under these sets of circumstances, the specific allergen may be an indirect or secondary etiologic factor in atopic dermatitis. As evidence and support of this third concept, the authors presented the results of their experiments in atopic individuals. An allergic contact dermatitis was produced in these patients by applying an extract of poison ivy. They were then exposed to intranasal, subcutaneous and surface application of specific allergens to which they had previously reacted by whealing with scratch tests. When this was done, they found that in most instances there was an exacerbation of the pre-existing allergic contact dermatitis. On the basis of this experiment, the authors suggested that the occasional beneficial effects of hyposensitization in atopic dermatitis can be explained as the result of the removal of such secondary aggravating factors. (Their experiments also lend support to the often noted clinical observation that hyposensitization with antigens to which the patient is sensitive, particularly when more concentrated doses are used, will frequently lead to an exacerbation of the dermatitis.)

The pruritus associated with atopic dermatitis has long been recognized as one of the major obstacles in the therapy of this disease. Arthur and Shelley[15] reviewed some of their outstanding experiments of pruritus. In their studies, the itch sensitivity and the itch time for patients with atopic dermatitis and other dermatidities of the hands were compared with those of normal subjects. The skin in atopic dermatitis was found to itch more readily and for a longer time than did normal skin. Although the hands were found to be an area naturally sensitive to itch stimuli, a great many variations in pruritus were shown to occur. They also demonstrated that the skin of atopic patients is apparently converted by the disease into one that is consistently highly sensitive to pruritogenic stimuli in certain areas of predilection.

The existence of pre-formed edema or of an enhanced exudatory response in skin of atopic dermatitis has previously been the subject of some controversy. Moller and Rorsman[16] studied the effect of intracutaneously injected histamine and of serum in twelve patients with atopic dermatitis and in twenty normal individuals. The exudatory responses were observed under a Wood's light after intravenous injection of sodium fluorescein, and it was found in the skin of patients with atopic dermatitis that the exudatory response was weaker than in the skin of normal individuals.

In some very interesting experiments, Allison and Bettley[17] demonstrated that the acantholytic effect of cantharidin is more marked in the eczematous than in the non-eczematous subject and furthermore this response is not

influenced by the oral administration of prednisone. In contrast to Moller's and Rorsman's findings, their studies showed a significantly greater exudation of fluid which contained a higher proportion of protein in the atopic subject than in the normal or in those individuals suffering from seborrheic, hypostatic or nummular eczema and urticaria. These results suggested to these authors that over and above any effect, direct or indirect, of cantharidin on capillary walls in the atopic subject, the vulnerable and damaged epidermal cells contribute something which affects the permeability of the vessel walls, and in turn influences the quantity and character of the plasma exudate. (If their results are confirmed, it would certainly suggest an important difference in the mechanism of eczema of the atopic variety and other forms of acquired eczema.)

In receiving the Borden Award for his research in fat metabolism, Hansen[18] reviewed his investigative studies on essential fatty acids in infant nutrition. For many years, Hansen studied the relationship of fat in the diet and in the circulation to the development of skin changes. A low iodine number, an index of unsaturated fatty acids, was found in patients with eczema as compared to control infants. On the basis of this finding and from observations that fat deficient diets in dogs led to eczematous skin lesions, he recommended the use of unsaturated fatty acids for the treatment of this condition and observed some possible beneficial effects from this form of treatment in atopic dermatitis. (Although clinically the use of unsaturated fatty acids for the treatment of atopic dermatitis in the reviewer's experience has not proved to be a very helpful adjunct in the management of this disease, it is interesting that some recent experimental work in mice has indicated that a variety of fatty acids, saturated, as well as unsaturated, are active in suppressing anaphylaxis and serotonin toxicity at low concentrations.[19])

On the basis of his previous experience and recent observations of ninety-five cases of atopic dermatitis in different age groups, Milder[20] discussed in general terms the significance of different factors contributing to the etiology of this disease.

Sedlis and Prose[21] studied 169 children with atopic dermatitis clinically and by pathological examination of skin biopsies. In their experience, the importance of food as an etiologic factor was very difficult to evaluate from the history. Twenty-four had received dietary treatment and only one mother claimed skin improvement as a result of such dietary changes. In substantiation with previous clinical observations that infants with eczema tend to be heavier, the authors found that forty-four of their patients were overweight. The clinical course was characterized by remissions and exacerbations, and it was frequently impossible to determine what etiologic factors contributed to this changing picture. Skin infection was a frequent complication. The program most frequently used for these children consisted of regular diets, sedation, soap substitutes and topical therapy consisting of a 5 per cent alcoholic solution of coal tar in a vanishing cream base. Sixty-nine biopsy specimens from the skin of thirty-nine patients with two types of eczema—the acute erythematous papular eruption and the chronic flexural type—revealed no changes specific for infantile eczema.

In contrast to the aforementioned study, Morris,[22] in a general review of atopic dermatitis, suggested that food plays a major role in the etiology of this condition.

In identification of the atopic individual, Jillson *et al*[23] discussed certain criteria—an extra fold of the lower eyelid (Dennie's Line), blanching after injection of acetylcholine or after local application of a nicotinic acid ester

ointment (Trafuril®), a distinctive histopathologic picture of localized intradermal vesiculation or spongiosis occurring after patch tests with certain substances and a positive cold pressor test. However, they stressed that no single criterion is invariably present or is diagnostic of the atopic state. The aforementioned criteria were applied to ten cases of contact dermatitis from neomycin and in six patients with contact dermatitis from ragweed oil. The authors hypothesized (without supportive evidence) that neomycin sensitivity will be found to occur predominantly, if not exclusively, in atopics. They also claimed that the "distinctive epidermal changes" associated with contact dermatitis in atopic individuals are described for the first time in ragweed oil contact dermatitis.

Most authors are almost unanimous in their opinions that psychogenic factors, either as a cause or as a secondary end result, play some role in atopic dermatitis. However, agreement stops there, with marked differences in opinion being expressed as to what extent the psychogenic factors contribute to the over-all picture of atopic dermatitis and as to whether extensive psychotherapy on some of these subjects is necessary. In a review paper, Wittkower and Hunt[24] summarized our present knowledge of the psychological aspects of atopic dermatitis in childhood. At the outset, these authors emphasized that these psychological aspects could be described as a part of the transactions of multiple foci relevant to the disorder. Examples of these foci given were hereditary, constitutional factors, allergic diathesis and psychodynamics. Part of the review is devoted to the literature relating to the atopic state and behavior anomalies observed. One factor in this regard is the general acceptance that the presence of the disfiguring disease affects the emotional interrelationship between the diseased child and the persons in his environment. Another consideration is the development of psychic phenomenon due to "noxious allergens." In this connection, the literature of the so-called "tension-fatigue syndrome" occurring in allergic individuals, and some of the investigations of electroencephalograms done in allergic children was reviewed. In another part of their review article, the authors discussed precipitating life situations, personality of the child with atopic dermatitis, child-parent relationships, and the psychopathology of emotional factors to allergic manifestations. The last section of the article dealt with the psychological therapeutic approach to this disorder. The authors emphasized that, although most cases of atopic dermatitis can be handled by the dermatologist and allergist, they can be more satisfactorily handled if these physicians are oriented along psychological lines; however, there are some cases which are severe enough to require additional care of a psychiatrist.

Rostenberg's[25] views of the psychosomatic concepts in atopic dermatitis can best be expressed by quoting directly from his conclusions: "What then can one say about the role of emotions in atopic dermatitis? I do not believe that any specific formulations can be made. I believe, and I have stated elsewhere, the emotional factors are only one facet of a dynamic interplay of factors conducive to pruritus in a genetically determined soil. The same inheritance that determines the dry quasi-ichthyotic skin with its vulnerability to pruriginous stimuli also determines that most people with such skins are atopic persons and may also favor a psychogenic maturation that in turn may lead to a commonness of emotional reactions to certain conflictual stimuli. To lift any one of these inherited determinants out of the total constellation of the syndrome of atopic dermatitis and to give it undue importance or to assign its pride of place so that it seems to dominate or to exercise a casual influence is to indulge in special pleading and

deserves Mencken's derisive comment. 'There is a solution for every human problem—neat, plausible, and wrong.' "

Bird[26] supported the theory that the hidden impulse in atopic dermatitis is anger. He illustrated by means of six case histories the importance of discovering the type of response which anger evoked in each patient, thus helping him to overcome the resulting expression on his skin. (The reviewers believe this to be an oversimplification of the psychodynamic factors present in this disease.)

The results of skin tests performed on 114 infants and children with eczema were analyzed by Ratner and Collins-Williams.[27] The subjects included forty-two infants under two years of age, thirty-eight older children with uncomplicated eczema and thirty-four infants and children with eczema complicated by respiratory allergy. Each patient was scratch tested with 350 different allergens, and additional intracutaneous tests were performed when the scratch tests to the pollens and inhalants were negative. Ninety-seven per cent of the group reacted to one or more of the allergens. A higher percentage of infants than older children reacted to foods alone. However, as the infants grew older, the inhalant and pollen sensitivities increased in frequency, and it was necessary to do repeated tests in order to uncover these new sensitivities. The order of frequency of activity in the infants was: egg, vegetables, inhalants, fish, fruits, meat, nuts, wheat, condiments, milk, cereal grains, pollens, bacteria, molds and chocolate. The order of frequency in older children was: vegetables, inhalants, fish, fruits, condiments, egg, nuts, bacteria, cereal grains, wheat, meats, pollens, milk, molds and chocolate. The authors postulated that the low order of frequency of milk allergy observed with the skin test reactions is attributable to the wide spread use of heat treated milks in infant feeding. The incidence of positive reactions to egg decreased markedly as the patients became older (a finding which has recently been confirmed by London and Glaser[28] in their studies of egg sensitive patients). The low incidence of positive reactions to chocolate, milk and wheat was stressed because these findings are contrary to the opinion of most allergists who regard these allergens as frequent offenders in eczema. The authors concluded that one must view the problem of eczema as a complex allergic phenomenon, and consideration must at all times be given to sensitizations encompassing the several groups of allergens—food, miscellaneous inhalants, pollens, molds and bacteria. They also stressed that the final interpretation of food sensitivity must rest on clinical corroboration of skin test reactions.

(We would certainly agree that the problem of eczema is indeed a complex allergic phenomenon and must also, at the same time, admit that in some instances our methods of management from the allergic approach has not been entirely satisfactory to cope with this problem. Although the reviewers' experiences have been similar to those of Ratner and Collins-Williams in the observation of a high incidence of positive skin test reactions in patients with atopic dermatitis, we have not always, unfortunately, experienced corresponding improvement in the eczema with the elimination of these foods. We cannot accept therefore, the concept that the use of additional or else a large number of skin tests is helpful in the management of this disease until better evidence is brought forth to indicate that the additional positive skin test reactions have in reality given information that facilitates the management of the patient.)

Grayson and Shair[29] reviewed the records of 106 patients with atopic dermatitis. Emotional disturbances were found to aggravate a pre-existing eruption in some of their cases. Of interest was the finding that the earlier

the onset of the dermatitis, the better the prognosis for freedom from eruption in adult life. They also stated that in order of effectiveness, the best therapeutic measures for the cutaneous manifestation of atopic dermatitis were (a) topical medication, (b) radiation (Grenz ray and x-ray), and (c) oral and parenteral medication. They also felt that hyposensitization was of limited value in the treatment of this condition. (The reviewers hold a strong opinion that there is no place for the use of x-ray in the treatment of atopic dermatitis in infants and children.)

A number of papers have been published concerning the therapy of atopic dermatitis. Kaufmann and Mayer[30] presented a general review of the treatment of all the allergic dermatoses, and Anning[31] discussed the drug treatment of eczema.

Litchfield[32] reported Pantho-F® Creme 0.2 per cent as being very effective in the treatment of both infantile eczema and intertriginous eruptions in diaper rash of early infancy. Topical therapy with chlorquinaldol, with and without hydrocortisone, has been reported as being effective in the therapy of eczematous lesions.[33,34] Another of the quinoline preparations, iodochlorhydroxyquin (Vioform®), in combination with hydrocortisone used both as a lotion and ointment, was also found to be a valuable adjunct in the treatment of eczematous dermatoses.[35] [In general, the reviewers have found the quinoline preparations to be most useful in the treatment of seborrheic dermatitis in infants. Chlorquinaldol (Sterosan®) has the advantage of leaving less of a yellowish stain on the skin.]

The use of sodium salicylate administered in 0.1 gm per kg body weight in divided doses was recommended by Guzhienko and Chekodanova[36] as a useful adjunct in the treatment of atopic dermatitis. Other measures ordinarily employed in the treatment of atopic dermatitis were used along with the sodium salicylate. (Although it is certainly not a panacea in the treatment of atopic dermatitis, the reviewers have also used acetylsalicylic acid as an adjunct in alleviating some of the severe pruritus characteristically associated with atopic dermatitis. Unlike the high doses previously mentioned, we use that dose ordinarily prescribed for analgesic and antipyretic effects.)

One of the more serious complications of atopic dermatitis is secondary infection of the lesions with vaccinia virus. The serious nature of this complication was well illustrated by Reynolds' and Joos'[37] report of nine cases of eczema vaccinatum including two fatalities. These authors rightfully emphasized that this disease is usually iatrogenic and recommended that the following steps be taken for prophylaxis: (1) no child with atopic dermatitis or other skin disorders should be vaccinated; (2) no child should be vaccinated if any member of his family has eczema or other skin disorder; (3) parents of children with eczema should be notified at the onset of the disease of the danger from vaccination contact; (4) if a sibling of a child with atopic dermatitis is vaccinated, he must be completely separated from the child for at least twenty-one days; (5) forms used by state and local health departments for parents' consent to vaccination should include an appropriate warning of the contraindications; (6) eczema vaccinatum should be a reportable disease; (7) patients recently vaccinated must be excluded from pediatric wards containing patients with atopic eczema, other diseases of the skin, burns or healing surgical incisions; (8) vaccination may be recommended at the age of two months especially for babies from strongly allergic families. It was of interest to note that of the nine cases reported by these authors, seven of the cases were caused by contact with a recently vaccinated sibling. The authors in this report also pointed out that hyper-immune

vaccinal gamma globulin is now available for specific therapy. (The hyperimmune gamma globulin preparation can be obtained from Dr. Henry C. Kempe, Chairman of the Department of Pediatrics, University of Colorado, Denver, Colorado.)

Ruppe *et al*[38] observed the case of a seventeen-year-old female patient who developed an acute herpetic infection superimposed upon her atopic skin lesion. The nature of the virus was identified by inoculation of mice with the vesicular fluid with the production of a meningoencephalitis and by complement-fixation tests. The administration of intramuscular injections of gamma globulin was thought to play an important role in the remarkable recovery of this patient.

Crawford,[39] in an article which contains many practical points, discussed the differential diagnosis, treatment and prognosis of allergic infantile eczema as compared to seborrheic infantile eczema. He properly emphasized that it is essential to differentiate atopic dermatitis and seborrheic dermatitis because of the differences in management and prognosis. For the atopic dermatitis he advocated an elimination diet for a short period, environmental control measures and hyposensitization. Other measures discussed were hospitalization, administration of unsaturated fatty acids, sedations, antihistamines, restraints and bandages, bathing, methods of combating secondary infection, and finally local therapy. With the exception of the proposed administration of various nutrients, such as B12 and B6 (the merit of which still remains to be proven), the treatment of seborrheic dermatitis is symptomatic in nature.

In an uncontrolled study, Nisenson[40] reported on the use of biotin in the treatment of fifteen patients with seborrheic dermatitis and two patients with Leiner's disease. In his paper, the author reviewed the previous literature with respect to these two diseases, which he believes are variations of the same disease and are due to a biotin deficiency. (Further controlled investigations will be necessary before a biotin deficiency can be accepted as the etiology of seborrheic dermatitis and Leiner's disease and before this vitamin is generally recommended for use in the treatment of these conditions.)

Letterer-Siwe's disease, by virtue of the waxy nature of the skin lesions, is occasionally mis-diagnosed as seborrheic dermatitis. Although this disease is very rare, Falk and Gellei,[41] in a study of two different families and a review of the literature, concluded that Letterer-Siwe's disease may occur as the result of a recessive gene in a homozygotic condition.

Because of the grave prognosis associated with the syndrome of eczema, thrombocytopenia and increased incidence of infection, a syndrome first described by Aldrich[42] which now bears his name, it is important to differentiate this clinical entity from other forms of allergic dermatoses. Krivit and Good,[43] in an excellent article, reviewed the clinical, hematological and pathological characteristics of Aldrich's Syndrome and reported seven additional cases. All of the authors' patients were boys, the syndrome apparently being transmitted as a sex-linked recessive trait. Rectal bleeding, purpura and petechiae were frequently recognized in the neonatal period and early in life. Immunological studies showed that in spite of the persistent thrombocytopenia, there were normal numbers and morphology of megakaryocytes. Peripheral and marrow eosinophilia were noted in five of the affected children. Furthermore, the bone marrow examinations, except for revealing a plasmacytosis and toxic changes among the neutrophils, were normal. Nonspecific and inflammatory changes were noted in the skin and lymph node biopsy specimens; however, post-mortem material in one patient and a

lymph node biopsy in another revealed multiple thromboses of the small arterioles. A fatal outcome was noted in all of the patients despite cortisone and ACTH therapy, splenectomy, and multiple types of antiallergic therapy. Because of the frequency and severity of infections noted, these authors made an extensive investigation of the defense mechanisms involved. This revealed no clear evidence of deficiency of the immune response to most antigens. The isoagglutinins were regularly absent in these children. Gamma globulin levels were normal or slightly elevated. Properdin levels were normal. Leukocyte function in the inflammatory reaction, migration and phagocytosis were within normal limits. A further study of the etiology of the thrombocytopenia revealed no platelet agglutinins and a normal production of platelets. The thrombocytopenia did not seem to correlate with the course of the eczema. As was mentioned earlier, all attempts of treatment of the disease were unsuccessful though both adrenal steroid therapy and systemic treatment with estrogen and progesterone ameliorated the eczematoid processes.

Cummins *et al*[44] reported the occurrence of this syndrome in three-and-a-half-year-old twins. In addition to thrombocytopenia, spontaneous bleeding, including ecchymoses and epistaxis, the twins were violently allergic. One spoonful of peas would produce bloody diarrhea. Turnips produced swelling of the joints. Touching the skin with an unbroken egg produced wheals, and the ingestion of goat's milk provoked immediate vomiting and wheezing. Steroids were partially effective in controlling the allergic manifestations but had very questionable effects on controlling the thrombocytopenia. As in the previous studies quoted, extensive studies of immune mechanism were unrevealing of the etiology of this syndrome. Studies directed at protein digestion, absorption and metabolism were also unrewarding.

Recently, another rare unreported syndrome consisting of chronic suppurative lymphadenitis, hepatosplenomegaly, pulmonary infiltrations and eczematoid dermatitis of characteristic distribution has been described in four male children by Bridges, Berendes and Good.[45] The manifestations of the syndrome are the result of a generalized granulomatous process and are associated with a prominent hypergammaglobulinemia. In their paper, the authors differentiate this new syndrome from recognized forms of infectious and non-infectious disease producing granulomatous processes in childhood. Extensive clinical, pathological and laboratory examinations that made this distinction possible were described. In spite of these extensive investigative studies, the nature of this syndrome remained obscure. Extensive empirical efforts at treatment of the disease were without effect upon the relentless progression that would seem to be the most characteristic feature of this syndrome.

### URTICARIA AND ANGIOEDEMA

Very few articles relating to urticaria and angioedema have appeared in the literature, and the papers published were primarily devoted to adult patients. Feinberg *et al*[46] made one helpful contribution to our therapeutic armamentarium of chronic urticaria by demonstrating that hydroxyzine gives relief in the majority of cases of chronic urticaria and dermographia. The dose of hydroxyzine used most frequently was 10 mgs three to four times daily. It was the authors' belief that relief in most cases exceeded that obtained with larger doses of antihistamines, sedatives or other potent tranquilizers. The results in acute urticaria were less dramatic. Of interest was their observation that some relief from itching was obtained in a number

of cases of atopic and other types of dermatoses. However, the effects of this drug on allergic rhinitis and asthma were less impressive. Because of the clinical results observed with the administration of this drug, experimental studies were also done on guinea pigs. From these studies the authors concluded that hydroxyzine in the guinea pig is an effective, long-acting, anti-anaphylactic, antihistaminic, anti-serotonin and anti-cholinergic drug.

In a study of fifty patients with chronic urticaria, Eisenberg[47] felt that this condition, with the exception of that caused by infection or drugs, is seldom due to a single factor but rather to multiple causes. He therefore recommended a "total" approach in the treatment of this condition. This included a comprehensive history and physical examination, sufficient laboratory work to exclude infectious processes, skin tests, and a reasonable psychological evaluation of the patient. In most of the fifty patients studied, 62 per cent of whom were females, the hives and itching could be controlled with antihistamines alone or in combination with ephedrine hydrochloride and tranquilizers. Emotional difficulties appeared to be significant in thirty-two patients, but among these there were only six in whom no other factors were clearly operative. By the use of this approach, the author stated that thirty-six (72 per cent) of his patients improved.

In the past, foci of infection and in particular dental infections, have been considered as possible etiologic factors in chronic urticaria. Resch and Evans[48] in a study of 100 patients with chronic urticaria found evidence of chronic dental infection in fifty of these subjects. After dental treatment of seventeen patients, urticaria was unchanged in eleven, was relieved in six with subsequent return of urticaria in three. The authors concluded that the course of the treated patients in this small series does not suggest a frequent or important relationship of dental infection to urticaria, although occasionally gratifying relief of symptoms may follow appropriate dental treatment.

A nine-year-old boy who developed erythema and urticaria whenever exposed to cold was described by Dieckhoff and Arndts.[49] These manifestations first occurred following an attack of typhoid fever. Positive transfer tests were demonstrated as well as increased acid gastric juice and plasma values for free histamine after exposure to cold. The histamine excretion in the urine remained uninfluenced by these experiments. The administration of prednisone seemed to have questionable therapeutic effects. However, the pruritus did seem to be less and the wheals were not as pronounced. In addition, the plasma concentration of histamine was markedly reduced after eight days of prednisone therapy. Antihistaminics, ascorbic acid and rutin apparently had no effect on the patient's reaction to cold.

Johnston and Cazort[50] presented a general discussion of their clinical observations of dermographia. They pointed out that dermographia is frequently overlooked and should be considered in any case of unexplained chronic urticaria. They also felt that the incidence of dermographia was increasing and that allergic reactions to penicillin frequently initiated the condition. Antihistaminics were recommended for therapy, but ACTH and steroids were thought to aggravate the dermographia. (Antihistaminics have not been very effective in the treatment of this condition in the reviewers' experience, nor have we noted any worsening of dermographia from the administration of corticosteroids.)

Although urticaria pigmentosa is not a hypersensitivity reaction, this condition is of interest to both the pediatric allergist and the pediatrician. Recently a number of informative reports have appeared in the literature in regard to this disease. Bloom *et al*[51] reported the occurrence of two epi-

sodes of acute spontaneous histamine shock in a three-months-old infant with urticaria pigmentosa. Following the surgical removal of two mastocytomas the histamine shocks disappeared, although numerous ordinary pigmentosa lesions still remained. Prior to surgery, the urinary excretion of histamine was markedly elevated. The urinary output of 5-hydroxytryptamine (serotonin), however, was found to be within normal limits.

Gardner[52] summarized our knowledge on the metabolic patterns of histidine and histamine metabolism. He postulated that urticaria pigmentosa might represent a biochemical error in the metabolism of an enzyme involved in the degradation of histamine or of heparin, and that the proliferation of mast cells represents a homeostatic reaction to provide an intracellular "storage" site for these compounds which are so potent when free in the plasma. Another possibility suggested was the excessive multiplication of mast cells due to a somatic mutation in that cell series. These postulations were partly based on the findings of markedly elevated levels of histamine and heparin-like compounds in the liver and spleen of a patient who had mast cell leukemia manifested by urticaria pigmentosa.[53]

Brogen *et al*[54] studied histamine and 5-hydroxyindolacetic acid urinary excretion in nine patients with urticaria pigmentosa. Skeletal changes, characterized by a diffuse and widespread osteosclerotic-osteoporotic process of pagetoid appearance, were observed roentgenographically in five of the nine patients. The studies on urinary excretion and 5-hydroxyindolacetic acid revealed a pronounced abnormal histaminuria in all nine of the patients, but no increase in the 5-hydroxyindolacetic acid. From the remarkable increase in urinary histamine excretion, the authors concluded that the mastocytes, which constitute the histopathological basis of the urticaria pigmentosa, produce excessive amounts of this substance. In one of their patients, the extirpation of a single cutaneous infiltrate was followed by a drop in the histaminuria to normal value. Because another patient showed severe intolerance to acetylsalicylic acid, the authors suggested that the acetylsalicylic acid acted as a histamine liberator in this particular patient.

A review of thirty-two children with urticaria pigmentosa by Lees and Stroud[55] also disclosed four patients with significant bone lesions attributed to mast cell infiltration. Two of these children showed changes similar to those seen in Scheuermann's disease, an association not previously described.

Because reserpine had been noted to produce degranulation of tissue mast cells, Baer *et al*[56] postulated that it might bring about clinically detectable changes in urticaria pigmentosa. Following the administration of reserpine to three patients suffering from this disease, they observed a decrease or disappearance of itching, burning and whealing, the fading of some of the lesions, and in one case a generalized Herxheimer reaction-like effect, indicating that reserpine had an effect on the lesions and subjective manifestations of urticaria pigmentosa. The authors suggested more extensive trials, but not in doses higher than 1 mg a day for one week and a maintenance daily dose of 0.25 mg.

An unusual syndrome was described by Heiner and Blitzer[57] which should be considered in the differential diagnosis of some cases of angioedema. They described two children and their father with paroxysmal symptoms which included a rash, angioedema, severe gastrointestinal and urinary tract symptoms and other evidence of autonomic nervous system dysfunction. Attempts at medicinal therapy failed to ameloriate the attacks. They noted a striking hereditary pattern suggesting a simple dominant type of inheritance. Emotional factors were found capable of precipitating these paroxysms which seemed to have many features in common with paroxysmal disorders

described in the literature under the terms periodic peritonitis, cyclic vomiting, hereditary angioedema and "periodic disease."

### CONTACT DERMATITIS

Hill,[58] in being honored by the Section of Allergy, American Academy of Pediatrics, for his untiring services as a pioneer investigator in the field of pediatric allergy, presented his studies of 200 consecutive cases of eczema in children. Fifty-three of these cases were thought to be caused by outside contact with allergic or irritating material. Of these, the etiology was determined in thirty-one cases, the probable cause was found in eighteen, and in four the etiology was not discovered. Clothes (including diapers and shoes) were incriminated in forty of the cases, and Hill concluded that contact eczema as seen in young children (in contrast to that seen in adults) is more likely to be due to clothing. It was also his feeling that in children, reactions occurred from a lesser degree of sensitivity and from primary irritants of relatively low irritating properties.

Waldbott[59] presented the diagnostic and therapeutic approaches to the child with skin lesions other than those typical of atopic eczema, which might possibly represent contact dermatitis. (His article was full of many "little pearls" from his own experience and contained many good illustrations.) Waldbott emphasized that the recognition of the etiology is the most important therapeutic tool because avoidance of irritants is the best possible therapy.

An unusual untoward contact-type of reaction to a new ceruminolytic agent was reported by Daschbach.[60] He described a two-year-old boy who developed two separate episodes of sudden swelling of the auricles following the installation of the ceruminolytic agent (Cerumenex®) into the ear canals. This child was a known asthmatic, suggesting to the author that his underlying allergic diathesis may have been a contributing factor in the observed reactions. (This report emphasizes the constant need for physician alertness in recognizing possible untoward reactions in the use of any new preparation, no matter how innocuous it may appear to be.)

Contact dermatitis due to poison ivy and related plants has been the subject of a number of reports. Two excellent comprehensive papers on poison ivy dermatitis have been written by Kligman.[61,62] In these articles Kligman discussed the botany, chemistry and cross reactions of the different rhus species. In addition, he reviewed the clinical biology, the incidence, duration and variability of sensitivity, the prevention, immunology, clinical features, topical prophylaxis and therapy of this disease.

Langs *et al*[63,64] reported their results with Aqua Ivy® tablets in the oral prophylaxis against poison ivy dermatitis. A controlled, "double-blind" study was carried out in 142 heavily exposed Coast Guardsmen, in an effort to evaluate the use of the Aqua Ivy® tablets as a means of providing oral prophylaxis against poison ivy dermatitis. Based on their data, the authors concluded that these tablets provide a safe and effective means of oral prophylaxis against this disease. (The authors, in discussing their own findings, point out several criticisms of their experimental procedure. Certainly before this preparation can be accepted as an effective agent for the oral prophylaxis of rhus dermatitis, more extensive studies will be necessary under better experimental conditions.)

Swarts and Rourke[65] have recently reported several untoward reactions from the oral administration of this preparation indicating that Aqua Ivy® may not be as completely free of untoward effects as suggested by Langs *et al.*

In an uncontrolled study Mitchell[66] also concluded that eighty-five of ninety-three patients (91 per cent) treated with an alcohol-soluble fraction (oleoresin) of the poison ivy leaf administered orally in gelatin capsules were adequately protected against poison ivy dermatitis. Lipton[67] recommended a topical application of *Impatiens biflora* (Jewelweed) in dilutions of 1:4 to subjects with rhus dermatitis. (The rationale for the use of Jewelweed was not explained, nor was any evidence presented that Jewelweed was more effective than simple compresses.)

### MISCELLANEOUS SKIN DISEASES

Several review articles covering some of the recent advances in the field of dermatology have been published.[2,68,69] Dermatologic problems commonly seen by pediatricians were discussed in general terms by Perlman and Falk[70] under the headings of eczematous dermatoses, pyodermas, and maculopapular squamous dermatoses.

A super-oiled, colloidal oatmeal was considered to be very useful as an adjunct in the therapy of various pruritic and dry skin conditions by Dick[71] and by Franks.[72]

Hughes and Hamilton[73] suggested that in some instances eczema, rhinitis and asthma may be the result of sensitization to human scurf. They obtained positive skin test reactions with *Pityrosporum ovale* and proposed the use of hyposensitization. (No conclusive evidence was offered by these authors proving any relationship between a positive skin test to *Pityrosporum ovale* and a clinical sensitivity. Without better evidence than that presented, the authors would be reluctant to institute a program of hyposensitization with *Pityrosporum ovale* or human dander.)

In the treatment of seborrhea of the scalp, Harvey and Ereaux[74] found cadmium sulfide shampoo to be effective in 75 per cent of 127 cases treated with this preparation. Caspers,[75] on the other hand, in a clinical evaluation of several different remedies for seborrhea of the scalp, found benzalkonium chloride (Sabol®) to be the most effective in the treatment of this condition. (The authors have also found that a similar preparation containing alkyl dimethyl-benzylammonium chloride (Rinse Away) to be extremely effective in the control of seborrhea of the scalp in older children.)

Because of its common occurrence and its frequent confusion with seborrheic dermatitis, moniliasis is of special interest to the pediatrician and allergist. In an excellent review on moniliasis Dobias[76] covered the various forms of this disease in the pediatric age group and discussed its pathogenesis, incidence, diagnosis and management. Dobias also mentioned some of the allergic manifestations of this disease, and as an example he cited a case of asthma in an infant. He attributed this case to extensive cutaneous, oral and vaginal moniliasis. The infant's asthma disappeared after oral administration of nystatin. The article contained eighteen excellent colored pictures illustrating the types of monilial infections. In addition there were 181 references. Yonis and Geifman[77] similarly presented a general review on moniliasis in infants. Kozinn and his co-workers,[78,79] in two articles on moniliasis, discussed the incidence and pathogenesis of this disease in the newborn. These authors found that factors commonly listed as contributory to oral thrush (such as debility and prematurity) were not found to be such in their studies. They did find, however, that maternal vaginal candidiasis appeared to be a primary source of the neonatal monilial infection. Harris *et al*[80] also found a high degree of correlation between positive vaginal cultures in pregnant women and the development of positive oral cultures in infants with clinical thrush. They proposed that thrush could be elimi-

nated from hospital nurseries by the simple, harmless and inexpensive procedure of instilling nystatin (Myostatin®) solution into the mouths of newborn babies. On the other hand, Vignec[81] was unable to demonstrate this maternal-infant relationship. In contrast to Kozinn's findings that *Candida albicans* occurs on the skin only as a pathogen, Vignec was able to recover *Candida* from the skin in 43.3 per cent of infants with rashes which were not attributed to monilia, such as eczema and seborrheic dermatitis.

In many areas, a 1 per cent aqueous solution of gentian violet continues to be used as the treatment for oral thrush in the neonatal period. Slotkowski[82] pointed out that the application of this preparation to the infant's mucous membranes for the management of thrush is not without danger. He demonstrated that prolonged use of this medication may result in the formation of mucous membrane lesions. (With a more effective drug, nystatin, available for the treatment of monilia infections, there no longer seems to be any need for the use of gentian violet in the treatment of oral moniliasis.)

Winkelmann[83] described the clinical and pathological findings in five cases of anaphylactoid purpura. One case was associated with exposure to the weed killer 2,4-D and one with injections of bacterial allergens. In the other three cases, no agent was implicated. Soto *et al*[84] also presented an extensive review of this disease and reported fifty-five cases of anaphylactoid purpura observed in the Children's Hospital of Mexico City from 1953 to 1956. These authors stressed the occurrence of renal involvement and observed that in a follow-up of their patients 12 per cent had chronic glomerulonephritis. It was their opinion that steroids should not be used indiscriminately in the treatment of this condition. Menzi[85] was of the opinion that ACTH and cortisone might be helpful in the symptomatic relief of the arthralgia and abdominal symptoms, but did not believe that the course of the renal complications was altered by the administration of these agents.

Steinhardt and Jonas[86] have again called our attention to intussusception as a rare complication of anaphylactoid purpura, which must constantly be borne in mind as a possible cause of some of the symptomatology observed in this syndrome. No symptom or sign of abdominal purpura clearly delineates the presence of an intussusception, but the authors felt that an obstruction, a mass, and the passage of blood rectally are indications for surgical intervention to rule out this complication.

Although the etiology of anaphylactoid purpura remains obscure, this condition has been associated with certain drugs, insecticides, foods, injections of serums, and streptococcal infections. Mann and Pasha[87] attributed a case of anaphylactoid purpura to a pulmonary infection with aspergillosis. The occurrence of this syndrome in siblings was also reported by Towner.[88] In one of the sibs, the syndrome appeared after immunization against diphtheria and pertussis, while in the other it followed an upper respiratory infection. Turin, Mandel and Hornstein[89] described a three-year-old girl who developed a fulminating purpura which culminated in gangrene of the left leg necessitating amputation. These authors felt that this child's disease was a variant of the anaphylactoid purpura syndrome. ACTH and antibiotic therapy were ineffectual in preventing or reversing the gangrenous process.

Foerster and Scott[90] reported a case of erythema multiforme exudativum (Stevens-Johnson syndrome) in which herpes simplex virus was isolated from the vesicular fluid and identified by serological techniques. A review was presented of previous studies in which this virus was implicated in the

pathogenesis of erythema multiforme exudativum. (From these reports it appears that erythema multiforme exudativum can, in some instances, be caused by the herpes simplex virus. However, many investigators have been unsuccessful in the isolation of the virus in this disease, and it seems likely that this entity probably has multiple factors contributing to its etiology.)

The relationship of skin pH to chronologic age in the newborn was studied by Behrendt and Green.[91] During the first two days of life, the majority of the newborn children showed abnormally "alkaline" skin pH. However, in the next few days of life there was a progressive increase in the percentage of newborns who fully developed skin acidity. Most of the infants seven days of age and older exhibited a normal acid skin pH. The authors postulated that the higher skin pH observed during the newborn period is most likely caused by the neutralizing influence of the vernix caseosa. They concluded that the mechanism affecting skin acidity is operating during early life.

The relationship of perianal dermatitis to fecal pH was investigated by Tanino, Steiner and Benjamin.[92] Data obtained from measurements of the pH of the stools in 434 patients failed to support the thesis that fecal alkalinity is a major factor in the genesis of perianal dermatitis.

Taylor and Bondurant[93] emphasized that erythema neonatorum allergicum, a dermatitis of the newborn consisting of papules and pustules appearing in the first three days of life and disappearing by the sixth day, is an extremely common condition in the newborn period. Of 200 consecutive newborn infants observed by the authors, sixty-two had this condition. Fluid from the pustules in these patients was found to contain 90 per cent eosinophils but not bacterial organisms by smear or culture. (The cause of erythema neonatorum allergicum remains obscure. Although a hypersensitivity reaction has been postulated, the eosinophilic response of the lesions should not be taken as evidence of its allergic origin since eosinophilia has been demonstrated to be a normal inflammatory response in the newborn and early infancy period.[94,95])

Kohlenbrener, Boehm and Falk[96] described the case of a two-months-old infant who had necrotic progression of pyoderma gangrenosum associated with otitis media. Although *Pseudomonas aeruginosa* was cultured from the lesions, the authors postulated that the Shwartzman phenomenon may have been the underlying mechanism producing the necrotic skin lesions.

## ASTHMA

A large number of publications on asthma and subjects relating to this disease have appeared during the period covered by this review. Some indication of the number of annually published papers concerning this disease can be obtained by referring to the excellent, comprehensive review of bronchial asthma by Unger and Johnson.[3] This review contains 106 pages of compact information with 675 references. As stated earlier, the present review will refer mainly to those papers on bronchial asthma that are primarily related to the pediatric age group and should by no means be interpreted as being a complete, exhaustive review of the subject.

The incidence of asthma in Copenhagen was studied by Frandsen.[97] Of 79,944 school children surveyed during the school year of 1949 to 1950, 643 (0.8 per cent) were diagnosed as having asthma. The incidence of the disease was highest from nine to twelve years of age in both the girls and boys; however, the ratio of boys to girls was approximately 2:1 (a similar preponderance of boys over girls has been frequently reported in this

country). Whereas the number of severe cases was approximately the same in either sex, there were almost twice as many boys as girls among the mild and moderate cases. A somewhat higher incidence of asthma was found among the children in private schools. One-fifth of the patients were absent from school for more than a quarter of the school year. In spite of prolonged non-attendance, however, one-third of the children were above-average in grades and less than one-sixth fell below the average. One-quarter of the boys and one-half the girls were wholly or partially excused from physical exercises, and the author considered this to be an unfortunate set of circumstances. One-sixth of the children were noted to have deformities of the thorax, emphysema and faulty posture. Because one-fourth of these asthmatic children had not been referred for specialist treatment of the disease, the author concluded that there was insufficient treatment for asthmatic school children in his locality.

Some of the clinical aspects of bronchial asthma in childhood were reviewed by Gottlieb.[98] The author pointed out that while in general there are many resemblances to the adult form of the disease, a number of areas of difference exist. Such distinctions stem largely from the child's physiological differences relating to the greater lability of homeostatic mechanisms; from anatomic differences, including greater molibity of the thorax and the stage of development of paranasal sinuses; from immunologic differences such as the poorer resistance to infection and the condition of immunologic immaturity; and from pharmacologic differences in drug tolerance and responsiveness. Accordingly, at the clinical level, the physician treating asthma in children should recognize the symptomatic pattern of the disease and the sometimes atypical physical findings. The author emphasized that the disorders to be taken into consideration in the differential diagnosis differ markedly from those in older age groups. The author further briefly discussed some of the hereditary influences, prophylactic approaches and outlined a program of therapy.

Buffum[99,100,101] in several articles, discussed the diagnosis and prognosis of asthma in infancy. Buffum particularly stressed the problem of differentiating asthma from other conditions in infancy. From his experience with seventy-nine wheezing infants under two years of age, he concluded that attacks of asthma more commonly occur with respiratory infections. Contrary to the generally accepted opinion that asthma in the beginning manifests itself in paroxysmal attacks with complete clearing in the intervals, patients in his series began with apparent respiratory infections and wheezed continuously for periods from one to several months. It is also interesting that more than half of these infants did not have significantly positive scratch tests. The author observed that the more marked the signs of allergy, as shown by the number and degree of positive tests and as shown by the severity of the eczema, the more intractable the asthma was likely to be.

In his article on the prognosis of asthma in infancy, Buffum[101] stated that this condition is both common and important in this age group. A follow-up of eighty-seven patients seen with asthma before the age of two years (now at an average age of nine years) indicated that forty-eight had not wheezed in the last year. Of the nineteen patients with asthma, atopic dermatitis and a positive skin test reaction to egg white, only three had not wheezed during the last year. Of the thirty patients with negative tests at the first testing and with no atopic dermatitis, twenty-one had no wheezing during the past year. From these findings Buffum concluded that the capacity to develop hypersensitivity varies in degree, that the patients with the greatest

capacity had the poorest prognosis, and that generally this capacity can be roughly estimated at the first visit. (Thus it appears that limited skin testing, particularly to egg white, during infancy has some value in determining the ultimate prognosis for infants affected with asthma.)

In addition to Buffum's observations, a number of other follow-up studies of asthmatic children have appeared in the recent literature. In a continued follow-up investigation, Ryssing[102] again evaluated the status of 298 asthmatic children who had been studied in 1944. Information was obtained concerning 281 out of 283 survivors. A review of these cases showed that those children in whom the disease commenced early, was of short duration, and disappeared before the age of fifteen years seemed to have the greatest chance of becoming permanently symptom-free. Only 106 (35.5 per cent) out of the 298 patients were free from symptoms at the time of evaluation, and only sixteen of these patients had received hyposensitization. In other words, only ninety patients (or approximately 30 per cent) had "grown out of" the disease or become symptom-free following various forms of nonspecific treatment. The author concluded that because only 30 per cent of children with asthma eventually and without specific treatment become symptom-free, early diagnosis, proper treatment, and continued observation are important in every case.

Von Harnack and Panten[103] in another follow-up study of 500 asthmatic children found that of 385 patients who had reached the age of sixteen years, 33.5 per cent were without symptoms and 16.1 per cent suffered from dyspnea without overt attacks of asthma. In support of Buffum's findings, children with eczema, urticaria and other allergic diseases had a worse prognosis. The authors felt that the most important factors in bringing on the asthmatic attacks were infections, weather, mental stress, fatigue, chill and allergens. Pearson[104] studied 625 patients with bronchial asthma when he attended two London hospital clinics for a period of six years. The remissions occurred most frequently during adolescence and the succeeding two decades. The natural history of the disease from this study indicated that most cases of asthma commenced during early life (40 per cent) and that allergic factors played an important role. With advance in age, those who did not improve spontaneously frequently developed infections which produced further complications of the asthma. A fatal outcome was rare in purely allergic asthma, but death did occur in those with repeated attacks of status asthmaticus.

In a twenty-year follow-up of 449 patients whose asthma began in childhood, Rackemann[105] found that 70 per cent were virtually symptom-free, that is, 30 per cent were completely free of symptoms, 20 per cent were symptom-free provided the offender was avoided, and 21 per cent had hay fever but no asthma. Another 15 per cent were having only mild asthmatic symptoms at the time of the evaluation, while only 11 per cent of the total were troubled by their symptoms. Eleven patients had died from various causes, four presumably from asthma. The average age at which the "cured" children became free of their asthmatic symptoms was 14.7 years. From this study Rackemann concluded that the prognosis of asthma in children is good.

Rackemann,[106] in another follow-up of 272 patients with "intrinsic" asthma, found that eighteen of these patients had some form of extrinsic "allergic" asthma in childhood. This was followed by an interval of several years during which the patient was free of his symptoms and later developed what was diagnosed as intrinsic asthma. In an additional paper (apparently a follow-up of the same 272 patients with intrinsic asthma previously

mentioned who were followed for a period of at least fifteen years) Rackemann[107] found that only about 20 per cent of these patients had remained free of asthma.

(From these follow-up studies it appears clear that at least 20 per cent to 30 per cent of children with bronchial asthma, irrespective of etiology, will have a spontaneous remission of the disease. However, these findings should not be construed by physicians as giving a "license" to tell parents that their child will "outgrow" his asthma and that allergic therapy is unnecessary.)

Brandner[108] discussed the pathogenesis and incidence of bronchial asthma in children. The author noted that since World War II there had been in his area an increased incidence of asthma which he attributed to physical and mental stress. As has been observed elsewhere, he noted asthma occurred more frequently in the male sex. Climate, weather and respiratory infections were thought to play a significant role in provoking attacks. Skin tests were considered to be a valuable aid for the diagnosis and management of the patient.

Williams *et al*,[109] in their study, assessed the relative importance of allergic, infective and psychological factors in 487 asthmatic patients of all ages. Considering the entire group, the author considered that the infective factor was present in 88 per cent, a psychological factor in 70 per cent and an allergic factor in 64 per cent. However, when these subjects were analyzed by age groups, the figures suggested that in infants (0 to five years) psychological factors appear to be the most important; in young adults (fifteen to twenty-four years) the allergic factor predominated; and in the forty-five years and older age group, the infective factor was by far the most important precipitating cause in the majority of the patients. Infection was also considered by Fagerberg[110] to be an important initial precipitating cause of both intrinsic (61.9 per cent) and extrinsic (42.8 per cent) asthma.

The importance of food allergy alone as a cause of bronchial asthma was again stressed by Rowe *et al*.[111]

A number of physiological studies have been performed in asthmatic children. Mitchell[112] studied the excretion of histamine acid phosphate administered subcutaneously to asthmatic children during acute attacks, to asymptomatic asthmatic children, and to non-allergic children. The mean percentages of the injected dose of histamine acid phosphate excreted as free histamine by the three groups were not significantly different. The results suggested to the author that there is no alteration in the rate of destruction or of removal from the plasma of histamine in asthma. He further concluded that if histamine is produced or released in excessive quantities in asthma, the normal or reduced output of free histamine in the urine during acute attacks must be attributed to abnormal retention of histamine in the tissues. Maas *et al*[113] also studied blood histamine levels in normal, allergic and tuberculous children. The authors found that the average histamine levels were similar in the three groups but that the allergic children showed a higher proportion of deviation from the average.

The fluctuation of arterial blood pressure was studied by Tyurin[114] in forty-six children with bronchial asthma. Measurements of the difference in arterial blood pressure between expiration and inspiration were noted. In normal children, in the absence of dyspnea, this difference was 3 to 5 mm; with minimal dyspnea, the inspiratory-expiratory difference was increased to 8 and 10 mm; in some of the severe cases, the difference was as much as 40 to 45 mm Hg. The author concluded that the inspiratory-expiratory blood pressure difference was an objective method of measuring

severity of dyspnea and bronchial asthma and that this difference usually precedes the onset of the acute attack.

Harnaes and Borgen[115] measured and compared the antistaphylolysin titers in the serum of 130 asthmatic children with a control group of fifty-eight children of similar ages. Significantly more asthmatic children had elevated antistaphylolysin titers. In the asthmatic group there was no significant difference in elevated titers among skin-test-positive and skin-test-negative patients, but there was a tendency toward higher titer values in the skin-test-negative group.

Bukantz and Berns[116] have reported their initial observations on the chemical nature and blood group substance content of asthmatic sputum. Chemical analysis of the sputa derived from fifty-three asthmatic subjects revealed a total carbohydrate (as glucose) of 6.2 to 28.2 per cent; nitrogen, 9.0 to 13.0 per cent; hexosamine, 11.0 to 15.0 per cent; fucose, 4.5 to 5.5 per cent; and total solids of 13.3 to 33.8 mg/ml. Chromatographic studies showed an amino acid pattern like that of most proteins with slightly larger quantities of threonine and phenylalanine and the demonstration of the following carbohydrates—galactose, mannose, fucose and hexosamine. A mucopolysaccharide was found chemically closely resembling blood group substance and possessing considerable blood group activity in hemagglutination inhibition studies. The authors also found that whole sputum was found to be antigenic in rabbits while the purified fractions were not.

Although the measurement of lung volumes is an established clinical and research tool in the investigation and evaluation of asthma, its use has not been generally adapted to asthmatic children. Two main reasons probably have accounted for this disusage in children: first, technical difficulties encountered in applying adult techniques of measuring lung volumes to children and, secondly, the lack of reliable normal standards. Recently, both of these difficulties, at least in the study of children over six years of age, have been partially overcome by the adaptation of the closed circuit helium dilution method to children and by the reporting of normal values in children by several groups of workers.[117-120]

Lung volumes of twenty-one asthmatic children were measured by Andrewes and Simmons[117] and compared to those observed in twenty-seven normal children and in four children with allergic rhinitis. The authors found that there was a very definite increase in the functional residual capacity (FRC) and residual volume in the asthmatic children, even as early as six-and-a-half years of age after an asthmatic history as short as six months. Hellieson *et al*[118] also reported the results of measurements of lung volumes and the mechanics of respiration in eighty-five normal children. Determination of lung volumes (residual volume, functional residual capacity, vital capacity and total lung capacity) correlated best with the individual's height and almost as well with the weight and surface area. Values for lung compliance correlated most closely with functional residual capacity and vital capacity.

In two separate papers Bernstein *et al*[119,120] reported complete lung volume and ventilatory studies in seventy normal children and fourteen in-patient asthmatic children shortly after their admission to the hospital and at varying times after treatment in the hospital. From the statistical analysis of the data obtained from the normal children, tables of predicted normal values for vital capacity, total lung capacity, functional residual capacity and maximum breathing capacity were prepared for boys and girls ranging in age from six to fourteen years. (These tables are available from Dr. Bernstein at a nominal fee to cover printing and handling expenses.) In the

majority of the chronic intractable asthmatic children, abnormalities in lung volumes, maximum breathing capacity and timed vital capacity, alone or in combination, were noted. Improvement in clinical status was not always accompanied by improvement in pulmonary function measurements. The one-second timed vital capacity determination alone did not appear to be a reliable predictor of pulmonary function in this study. Furthermore, there was very little correlation between the one-second timed vital capacity and the maximum breathing capacity. The functional residual capacity, the total lung capacity, and the FRC/TLC ratio proved to be useful indices of hyperinflation in this group of asthmatic children. The authors concluded that pulmonary function measurements provide the clinician with objective criteria of prognosis and response to treatment in childhood asthma.

Engstrom, Karlberg and Kraepelien and others have done extensive pulmonary function studies in both normal and allergic children and have reported their findings in a series of articles, most of which were published in *Acta Paediatrica*. Their first paper[121] was concerned with determining lung volumes in healthy children ranging in age from six to fourteen years. The functional residual capacity was measured by a modified closed circuit method with helium as a test gas. The relationships of lung volumes to weight, height and sitting height were determined by regression calculations; of the three body measurements, height proved to be the most favorable. Compared to girls, the boys showed a tendency toward higher values, but it was not possible to show a statistically significant difference. The ratio of functional residual capacity to total lung capacity and residual volume to total lung capacity and their relationship to age were calculated. A diagram for predicting the different lung volumes for height measurements was also presented.

In the second of their articles[122] the authors described the lung volumes in ninety-eight asymptomatic asthmatic children (sixty-six boys and thirty-two girls from six to fourteen years of age). The patients were classified in three groups according to the frequency of asthmatic attacks. The first group consisted of thirty-nine children with mild asthma who had less than five short attacks a year. Group two consisted of twenty-five children with moderately severe asthma with five to ten attacks of asthma per year. The third group was made up of thirty-four children with severe asthma with either more than ten attacks of wheezing per year or prolonged status asthmaticus. The different lung volumes in relation to height and the ratios FRC/TLC and RV/TLC in relation to age were compared with those for healthy children. FRC, RV, and TLC and both the ratios were significantly higher than those in healthy children, indicating a hyperinflation of the lungs. The changes in lung volumes also seemed to correlate to the frequency of attacks. In all three groups, however, there were some individual patients with lung volumes similar to those found in healthy children.

In their third article, Kraepelien[123] described the lung volumes in children with atopic dermatitis. Sixteen children ranging in age from seven to thirteen years who had atopic dermatitis without respiratory symptoms were studied. Fifteen of these children had lung volumes comparable to those found in healthy children, and therefore the author concluded there were no grounds for stating that an allergic constitution as such would cause changes in lung volumes.

The fourth of this series of articles was concerned with the effect of bronchodilator drugs on lung volumes in symptom-free asthmatic children.[124] Symptom-free asthmatic children with an elevated ratio of residual volume to total lung capacity were studied before and after the administration of

bronchodilator drugs. Fifteen children (ten boys and five girls) were administered Isoprenaline (Rx) in aerosol form and fifteen (ten boys and five girls) aminophylline intravenously. A significant lowering of residual volume, functional residual capacity (only after Isoprenaline®) and vital capacity was observed after administration of the drugs, but there were still distinct signs of hyperinflation. The effect appeared to be greater with Isoprenaline than after aminophylline. Because of their findings, the authors stressed the importance of prolonged treatment with bronchodilator drugs even during symptom-free periods.

In their fifth paper, the authors described the results of maximum breathing capacity in forty-six healthy and in nineteen symptom-free asthmatic children.[125] The symptom-free asthmatic children as a group showed a significantly decreased maximal breathing capacity and breathing reserve indicating a slight ventilatory insufficiency; however, an assessment of individual cases was made difficult by the great variations observed among the healthy children.

In the sixth paper, the techniques for determining both the one-second vital capacity and the total vital capacity were described.[126] The ratio of these two values was determined in seventeen healthy children from seven to twelve years of age and in thirty-eight symptom-free asthmatic children ranging in age from six to fourteen years. The symptom-free asthmatic children generally gave lower values as a sign of bronchial obstruction. Significantly, those who were severe asthmatics had the lowest values. The authors found the procedure was simple, took very little time and was of minimal annoyance for the child.

In the seventh article in their series on respiratory studies, the authors reported the results of a longitudinal study of lung volumes in asthmatic children during symptom-free periods.[127] The lung volumes of eighteen of the asthmatic children (nine boys and nine girls) with initially elevated ratios of residual volume to total lung capacity were re-examined during symptom-free periods after intervals of about two and four years. In these later examinations, the original hyperinflation had successively diminished and at the last examination the lung volumes did not differ markedly from those of healthy children. The general clinical improvement observed in the children between the first and last examination was closely analogous to the changes in lung volumes demonstrated during the same period. The results suggested that the hyperinflation demonstrated earlier is of functional origin and thus reversible. The authors concluded that successful normalization of the lung volumes is a hopeful prognostic sign. In the light of these findings, Kraepelien[128] in another paper discussed the prognosis for asthma in children.

In the last of these articles on pulmonary function in normal and allergic children, the authors presented their findings on the mechanics of breathing in asthmatic patients following provocation tests.[129] The mechanics of breathing were studied by simultaneously recording the tidal volume and related intraesophageal pressure changes, representing the changes of the intrapleural pressure. After a record of their regular breathing curve was made the patient was given a suspected allergen in aerosol form. In certain cases, distinct clinical symptoms appeared during provocation, and the airway resistance showed a marked increase. An increase in the airway resistance was also recorded in some cases in which no clinical symptoms were observed during the provocation. Where clinical symptoms occurred, they rapidly disappeared after inhalation of Isoprenaline® and simultaneously a rapid lowering of the airway resistance was recorded.

Other techniques, which were recently described by Oliver *et al*[130] might prove to be useful in measuring pulmonary ventilation in the younger age groups. These authors described a spirometer adapted for measurement of pulmonary ventilation in small infants. Forty-eight normal infants ranging in age from three days to three and nine-tenths months were studied and their values given in detail. (From the aforementioned studies on pulmonary function, it is apparent that these measurements can serve as a useful, objective means of evaluating therapeutic measures, the degree of pulmonary impairment, and the prognosis in children with asthma.)

## REFERENCES


1. Collins-Williams, C. and Ratner, B.: Pediatric allergy. A critical review. Ann. Allergy, 16:174, 1958.
2. Fromer, J. L.: Dermatologic allergy V. Ann. Allergy, 17:76, 1959.
3. Unger, L. and Johnson, J. H.: Bronchial asthma VI, Critical review of literature. Ann. Allergy, 17:429, 537 and 664, 1957.
4. Blatt, H.: Third review of microbial allergy, 1956-57. Rev. Allergy, 12:205, 1958.
5. Blatt, H.: Fourth review of microbial allergy, 1957-1958. Rev. Allergy, 13(2):133, 1959.
6. Henderson, L. L.: Hypersensitivity: Newer methods of investigation. Proc. Staff Meet. Mayo Clin., 33:459, 1958.
7. Burdon, K. L.: Enzyme activation in allergic reactions. Ann. Allergy, 16:168, 1958.
8. Burnett, M.: Auto-immune disease. I. Modern immunological concepts. Brit. M. J., 645 (Oct. 10) 1959. II. Pathology of the immune response. Brit. M. J., 720 (Oct. 17) 1959.
9. Swineford, O. and Agee, B. A.: The Arthus phenomenon. Rev. Allergy, 12:54, 1958.
10. Ungar, G. and Hayashi, H.: Enzymatic mechanisms in allergy. Ann. Allergy, 16:542, 1958.
11. Rich, A. R.: Studies on hypersensitivity. Canad. M. A. J., 78:163, 1958.
12. Editorial: Auto-immunity as cause of disease. Brit. M. J., p. 747 (Oct. 17) 1959.
13. Hamilton, J. D.: Tissue lesions in hypersensitivity. Canad. M.A.J., 78: 834, 1958.
14. Strauss, J. S. and Kligman, A. M.: The relationship of atopic allergy and dermatitis. A.M.A. Arch. Dermat., 75:806, 1957.
15. Arthur, R. P. and Shelley, W. B.: The nature of itching in dermatic skin. Ann. Int. Med., 49:900, 1958.
16. Möller, H. and Rorsman, H.: Studies on vascular permeability factors with sodium fluorescein. I. The effect of intracutaneously injected histamine; human serum and its protein fractions in normal individuals. II. The effect of intracutaneous injected histamine and serum in patients with atopic dermatitis. Acta dermat.-venerol., 38:233, 243, 1958.
17. Allison, J. H. and Bettley, F. R.: Investigations into cantharidin blisters raised on apparently normal skin in normal and abnormal subjects. Brit. J. Dermat., 70:331, 1958.
18. Hansen, A. E.: Essential fatty acids and infant nutrition. Pediatrics, 21:494 1958.
19. Ganley, O. H. and Robinson, H. J.: Antianaphylactic and antiserotonin activity of a compound obtained from egg yolk, peanut oil, and soybean lecithin. J. Allergy, 30:415, 1959.
20. Milder, E.: Atopic dermatitis (generalized neurodermatitis): the atopic dermatitis-asthma-hay fever syndrome. M. J. Australia, 1:72, 1958.
21. Sedlis, E. and Prose, P.: Infantile eczema with special reference to the pathologic lesion. Pediatrics, 23:802, 1959.
22. Morris, G. E.: Atopic dermatitis. Role of food allergy. Ann. Allergy, 16:599, 1958.
23. Jillson, O. F., Curwen, W. L. and Alexander, B. R.: Problems of contact dermatitis in the atopic individual, with reference to neomycin and ragweed oil sensitivity. Ann. Allergy, 17:215, 1959.
24. Wittkower, E. D. and Hunt, B. R.: Psychological aspects of atopic dermatitis in children. Canad. M. A. J., 79:810, 1958.

25. Rostenberg, A.: Psychosomatic concepts in atopic dermatitis—a critique. A.M.A. Arch. Dermat., 79:118, 1959.
26. Bird, B.: Certain observations upon the relationship of anger and eczema. Am. Pract. & Digest Treat., 9:929, 1958.
27. Ratner, B. and Collins-Williams, C.: Analysis of protein skin reactivity in infants and childhood eczema. A.M.A. J. Dis. Child., 96:184, 1958.
28. London, R. L. and Glaser, J.: The cutaneous reaction to eggwhite. Pediatrics, 24:1009, 1959.
29. Grayson, L. D. and Shair, H. M.: Atopic dermatitis: A review of eight years. Part II. Ann. Allergy, 17:57, 1959.
30. Kaufmann, M. and Mayer, L. D.: The symptomatic treatment of allergic dermatoses. J. Kentucky M. A., 56:554, 1958.
31. Anning, S. T.: Drug treatment of eczema. Brit. M. J., 1087, 1959.
32. Litchfield, H. R.: The treatment of interriginous eruptions (diaper rash) and infantile eczema. Arch. Pediat., 76:73, 1959.
33. Fortier, D. and Gregoire, Y.: Clinical evaluation of sterosan in infantile eczema. Canad. M. A. J., 77:1035, 1957.
34. Fox, H. H.: Topical therapy with chlorquinaldol and hydrocortisone. Antibiotic Med., 6:85, 1959.
35. Montgomery, R. M. and Lavette, W. M.: Topical use of vioformhydrocortisone in dermatology. Clin. Med., 6:29, 1959.
36. Guzhienko, G. N. and Chekodanova, M. M.: Use of Na salicylate in the treatment of eczema. Pediatriya, 11:7, 1958.
37. Reynolds, A. H. and Joos, H. A.: Eczema vaccinatum. Pediatrics, 22:259, 1958.
38. Ruppe, J. P., Jr., Wilson, E. F., Jr. and Wolins, W.: Treatment of eczema herpeticum with gamma globulin. Arch. Dermat., 76:572, 1957.
39. Crawford, L. V.: Treatment of allergic eczema versus seborrheic infantile eczema. J. Pediat., 53:99, 1958.
40. Nisenson, A.: Seborrheic dermatitis of infants and Leiner's disease: A biotin deficiency. J. Pediat., 51:537, 1957.
41. Falk, W. and Gellei, B.: The familial occurrence of Letterer-Siwe disease. Acta paediat., 46:471, 1957.
42. Aldrich, R. A., Steinberg, A. G. and Campbell, D. C.: Pedigree demonstrating a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis, and bloody diarrhea. Pediatrics, 13:133, 1954.
43. Krivit, W. and Good, R. A.: Aldrich's syndrome (thrombocytopenia, eczema, and infection in infants). Studies of the defense mechanisms. A.M.A. J. Dis. Child., 97:137, 1959.
44. Cummins, L., Searer, W., Levenson, S., and Geppert, L.: Aldrich syndrome in twins. A.M.A. J. Dis. Child., 98:579, 1959.
45. Bridges, R. A., Berendes, H. and Good, R. A.: A fatal granulomatous disease of childhood. A.M.A. J. Dis. Child., 27:387, 1959.
46. Feinberg, A. R., Pruzansky, J., Feinberg, S. M. and Fisherman, E. W.: Effect of hydroxyzine (atarax) in chronic urticaria, respiratory allergies and atopic dermatitis. Clinical and experimental studies. J. Allergy, 29:358, 1958.
47. Eisenberg, B. C.: Management of chronic urticaria. J.A.M.A., 169:1, 1959.
48. Resch, C. A. and Evans, R. R.: Chronic urticaria and dental infection. Cleveland Clin. Quart., 25:147, 1958.
49. Dieckhoff, J. and Arndts, C. M.: Pathogenesis of urticaria due to cold. Allergie Asthma, 5:131, 1959.
50. Johnston, T. G. and Cazort, A. G.: Dermographia. Clinical observations. J.A.M.A., 169:91, 1959.
51. Bloom, G., Duner, H., Pernow, B., Winberg, J. and Zetterstrom, R.: Spontaneous histamine shocks in urticaria pigmentosa. Acta paediat., 47:113, 1958.
52. Gardner, L. I.: Emerging patterns of organic metabolism: with special reference to histamine. J. Allergy, 30:479, 1959.
53. Gardner, L. I. and Tice, A. A.: Histamine and related compounds in urticaria pigmentosa: Analyses of tissues having mast-cell infiltration. Pediatrics, 21:805, 1958.
54. Brogen, H. D., Duner, H., Hamrin, B., Pernow, B., Theander, G. and Waldenstrom, S.: Urticaria pigmentosa (mastocytosis): A study of nine cases with special reference to the excretion of histamine in urine. Acta med. scandinav., 163:223, 1959.
55. Lees, M. H. and Stroud, C. E.: Bone lesions of urticaria pigmentosa in childhood. Arch. Dis. childhood, 34:205, 1959.

56. Baer, R. L., Bersani, R. and Perzig, A.: Preliminary and short report. The effect of reserpine on urticaria pigmentosa. J. Invest. Dermat., 32:1, 1959.
57. Heiner, D. C. and Blitzer, J. R.: Familial paroxysmal dysfunction of the autonomic nervous system (a periodic disease), often precipitated by emotional stress. Pediatrics, 20:782, 1957.
58. Hill, L. W.: The importance of contact eczema in children. Pediatrics, 23: 797, 1959.
59. Waldbott, G. L.: Contact dermatitis in children. Internat. Arch. Allergy, 12:273, 1958.
60. Daschbach, R. J.: Untoward reaction to a new ceruminolytic agent. A.M.A. J. Dis. Child., 98:776, 1959.
61. Kligman, A. M.: Hyposensitization against rhus dermatitis. A.M.A. Arch. Dermat., 78:47, 1958.
62. Kligman, A. M.: Poison ivy (rhus) dermatitis. An experimental study. A.M.A. Arch. Dermat., 77:149, 1958.
63. Langs, R. J. and Straus, M. B.: Oral prophylaxis against poison ivy dermatitis with aqua ivy tablets. I. Controlled experiment and preliminary clinical report. J. Allergy, 30:130, 1959.
64. Langs, R. J., Fuchs, A. M. and Strauss, M. B.: Poison ivy dermatitis. Indust. Med., 28:257, 1959.
65. Swarts, W. B. and Rourke, T. A.: Reactions to orally administered poison ivy extract. J.A.M.A., 170:1409, 1959.
66. Mitchell, W. F: Poison ivy prophylaxis: folklore or scientific medicine? Ohio M. J., 55:797, 1959.
67. Lipton, R. A.: The use of Impatiens biflora (Jewelweed) in the treatment of rhus dermatitis. Ann. Allergy, 16:526, 1958.
68. Downing, J. G.: Medical progress, dermatology. New England J. Med., 260: 1170, 1959.
69. Duncan, A. G.: Recent advances in dermatologic therapy. Canad. M. A. J., 78:139, 1958.
70. Perlman, H. H. and Falk, A. B.: Pediatric dermatology. Report of a round table discussion. Pediatrics, 21:502, 1958.
71. Dick, L. A.: Colloidal emollient baths in pediatric dermatoses. Arch. Pediat., 75:506, 1958.
72. Franks, A. G.: Dermatologic use of baths. Am. Pract. & Digest Treat., 9:1998, 1958.
73. Hughes, W. H. and Hamilton, E. D.: Pityrosporum ovale as a cause of allergy to human scurf. Brit. M. J., 542 (Aug. 30) 1958.
74. Harvey, J. H. and Ereaux, L. P.: Clinical study of cadmium sulfide shampoo. Canad. M. A. J., 79:917, 1958.
75. Caspers, A. P.: Pityriasis capitis (dandruff). A clinical evaluation of three remedies currently employed in the prophylaxis and treatment of a common scalp disorder. Canad. M. A. J., 79:113, 1958.
76. Dobias, B.: Moniliasis in pediatrics. A.M.A. J. Dis. Child., 94:234, 1957.
77. Yonis, Z. and Geifman, M.: Moniliasis in infants. Harefuah, 54:83, 1958.
78. Kozinn, P. J., Taschdjian, C. L., Dragutsky, D. and Minsky, A.: Cutaneous candidiasis in early infancy and childhood. Pediatrics, 20:820, 1957.
79. Kozinn, P. J., Taschdjian, C. L. and Wilner, H.: Incidence and pathogenesis of neonatal candidiasis. Pediatrics, 21:421, 1958.
80. Harris, L. J., Pritzker, H. G., Laski, B., Eisen, A., Steiner, J. W. and Shack, L.: The effect of nystatin (Mycostatin) on neonatal candidiasis (thrush). Canad. M. A. J., 79:891, 1958.
81. Vignec, A. J.: The role of Candida albicans in the common skin disorders of infancy and early childhood. J. Pediat., 53:692, 1958.
82. Slotkowski, E. L.: Formation of mucous membrane lesions secondary to prolonged use of one per cent aqueous gentian violet. J. Pediat., 51:652, 1957.
83. Winkelmann, R. K.: Clinical and pathologic findings in the skin in anaphylactoid purpura (allergic angiitis). Proc. Staff Meet. Mayo Clin., 33:277, 1958.
84. Soto, R., Gordillo, G., Uribe, F. and Gonzalez, P.: Acute vascular purpura and its renal lesions. Boletin médico del Hospital infantil, 15:619, 1958.
85. Menzi, P.: ACTH and cortisone therapy in Schoenlein-Henoch's purpura. Ann. paediat., 190:94, 1958.
86. Steinhardt, I. D. and Jonas, A. F.: Coexistence of intussusception and Henoch's purpura. New England J. Med., 257:553, 1957.
87. Mann, B. and Paska, M. A.: Allergic primary pulmonary aspergillosis and Schönlein-Henoch purpura. Brit. M. J., 282 (Jan. 31) 1959.

88. Towner, C. H.: Familial incidence of the Henoch-Schönlein syndrome. Brit. M. J., 1385 (Dec. 19) 1959.
89. Turin, R. D., Mandel, S. and Hornstein, L.: Fulminating purpura with gangrene of lower extremity necessitating amputation. J. Pediat., 54:209, 1959.
90. Foerster, D. W. and Scott, L. V.: Isolation of herpes simplex virus from a patient with erythema multifore exudativum (Stevens-Johnson syndrome). New England J. Med., 259:476, 1958.
91. Behrendt, H. and Green, M.: Skin pH pattern in the newborn infant. A.M.A. J. Dis. Child., 95:35, 1958.
92. Tanino, J., Steiner, M. and Benjamin, B.: The relationship of perianal dermatitis to fecal pH. J. Pediat., 54:793, 1959.
93. Taylor, W. B. and Bondurant, C. P., Jr.: Erythema neonatorium allergicum. A.M.A. Arch. Dermat., 76:591, 1957.
94. Eitzman, D. V. and Smith, R. T.: The nonspecific inflammatory cycle in the neonatal infant. A.M.A. J. Dis. Child., 97:326, 1959.
95. Matheson, A., Rosenblum, A., Glazer, R., and Dacanay, E.: Local tissue and blood eosinophilia in newborn infants. J. Pediat., 51:502, 1957.
96. Kohlenbrener, R. M., Boehm, J. J. and Falk, A. B.: Pyoderma gangrenosum, Pseudomonas infection versus the Swartzman phenomenon. A.M.A. J. Dis. Child., 96:741, 1958.
97. Frandsen, S.: Bronchial asthma among school children in Copenhagen. Acta allerg., 12:341, 1958.
98. Gottleib, P. M.: Bronchial asthma in childhood. Internat. Arch. Allergy, 12:191, 1958.
99. Buffum, W. P.: The diagnosis of asthma in infancy. J. Pediat., 52:264, 1958.
100. Buffum, W. P.: Asthma in infancy. Rhode Island M. J., 41:134, 1958.
101. Buffum, W. P.: The prognosis of asthma in infancy. J. Allergy, 30:165, 1959.
102. Ryssing E.: Continued follow-up investigation concerning the fate of 298 asthmatic children. Acta paediat., 48:255, 1959.
103. Von Harnack, G. A. and Panten, B.: Bronchial asthma in childhood. Results of a follow-up study of 500 patients. Monatsschr. Kinderh., 105:255, 1957.
104. Pearson, R. S. B.: Natural history of asthma. Acta allergol., 12:277, 1958.
105. Rackemann, F. M.: The prognosis of asthma in children. Pediat. Clin. North America, 6:725, 1959.
106. Rackemann, F. M.: Asthma is a constitutional disease. J. Allergy, 29:535, 1958.
107. Rackemann, F. M. and Edwards, M. C.: Is intrinsic asthma a reversible disease? J. Allergy, 29:528, 1958.
108. Brandner, R.: The pathogenesis of bronchial asthma. Deutsche med. Wchnschr., 82:2032, 1957.
109. Williams, D. A., Lewis-Faning, E., Rees, L., Jacobs, J. and Thomas, A.: Assessment of the relative importance of the allergic, infective and psychological factors in asthma. Acta allergol., 12:376, 1958.
110. Fagerberg, E.: Infection for the first onset of asthma. Acta allergol., 12:17, 1958.
111. Rowe, A. H., Rowe, A., Jr. and Young, E. J.: Bronchial asthma due to food allergy alone in ninety-five patients. J.A.M.A., 169:1158, 1959.
112. Mitchell, R. G.: Excretion of injected histamine by asthmatic children. J. Allergy, 30:506, 1959.
113. Maas, J. W., Fehmers, G. A. and Strengers, T.: Studies on histamine. VII. Some aspects of blood histamine in normal, allergic and tuberculous children. Acta allergol, 10:170, 1956.
114. Tyurin, N. A.: Fluctuation of arterial blood pressure in bronchial asthma. Pediatriya, 8:41, 1957.
115. Harnaes, J. R. and Borgen, P. H. F.: Antistaphylolysin determinations in the sera of children with bronchial asthma. Acta allergol., 12:336, 1958.
116. Bukantz, A. C. and Berns, A. W.: Studied with sputum. I. Initial observations on the chemical nature and blood group substance content of asthmatic sputum. J. Allergy, 29:29, 1958.
117. Andrewes, J. F. and Simmons, D. H.: Lung volumes of normal and asthmatic children. Pediatrics, 23:507, 1959.
118. Hellieson, P. J., Cook, C. D., Friedlander, L. and Agathon, S.: Respiratory physiology in children. Pediatrics, 32:80, 1958.
119. Bernstein, I. L., Fragge, R. G., Gueron, M., Kreindler, L. and Ghory, I. E.: Pulmonary function in children. I. Determination of norms. J. Allergy, 30:514, 1959

120. Bernstein, I. L., Kreindler, L., Ghory, J. E., Fragge, R. G. and Gueron, M.: Pulmonary function in children. II. Preliminary studies in chronic intractable childhood asthma. J. Allergy, 30:534, 1959.
121. Engstrom, I., Karlberg, P. and Kraepelien, S.: Respiratory studies in children. I. Lung volumes in healthy children 6-14 years of age. Acta paediat., 46:277, 1956.
122. Kraepelien S., Engstrom, I. and Karlberg, P.: Respiratory studies in children. II. Lung volumes in symptom-free asthmatic children 6-14 years of age. Acta paediat., 47:399, 1958.
123. Kraepelien, S.: Respiratory studies in children. III. Lung volumes in children with prurigo besnier. Acta paediat., 47:412, 1958.
124. Kraepelien, S.: Respiratory studies in children. IV. The effect of bronchodilator drugs on the lung volumes in symptom-free asthmatic children. Acta paediat., 47:349, 1958.
125. Engstrom, I., Karlberg, P., Kraepelien, S. and Wengler, G.: Respiratory studies in children. V. Maximal breathing capacity in healthy and in symptom-free asthmatic children, 7-14 years of age. Acta paediat., 47:560, 1958.
126. Engstrom, I., Escardo, F. E., Karlberg, P. and Kraepelien, S.: Respiratory studies in children. VI. Timed vital capacity in healthy children and in symptom-free asthmatic children. Acta paediat., 48:114, 1959.
127. Kraepelien, S.: Respiratory studies in children. VII. A longitudinal study of the lung volumes in asthmatic children during symptom-free periods. Acta paediat., 48:335, 1959.
128. Kraepelien, S.: Viewpoints concerning the prognosis for asthma in children in the light of respiration studies. Acta allergol., 12:215, 1958.
129. Engstrom, I., Karlberg, P., Koch, G. and Kraepelien, S.: Use of analysis of mechanics of breathing in provocation test in bronchial asthma. Acta paediat., 47:441, 1958.

*(To be continued in the December issue)*

---

## THE BINOMINAL THEORY OF TAXONOMY

All things are not within the immediate reach of human capacity. Many have been made known to us, of which those who went before us were ignorant; many we have heard of, but know not what they are; and many must remain for the diligence of future ages.

It is the exclusive property of man, to contemplate and to reason on the great book of nature. She gradually unfolds herself to him, who with patience and perseverance, will search into her mysteries; and when the memory of the present and of past generations shall be entirely obliterated, he shall enjoy the high privilege of living in the minds of his successors, as he has been advanced in the dignity of his nature, by the labours of those who went before him.—LINNAEUS (1707-1778) *Systema Naturae.* Trans. by W. TURTON, (from *Moments of Discovery. The Development of Modern Science.* Edited by GEORGE SCHWARTZ and PHILIP BISHOP, Basic Books, Inc., 1958, New York.)

# News Items

### PERU SOCIETY OF ALLERGY

The Peru Society of Allergy recently elected new directors for 1960. They are as follows:

President.....José Zegarra Puppi, M.D.
First Vice President.....Eduardo Cánepa, M.D.
Secretary General.....Gustavo Delgado Matallana, M.D.

### DOCTOR GLASER HONORED

Dr. Jerome Glaser of Rochester, New York, was honored by the Section on Allergy of the American Academy of Pediatrics at a meeting held in Chicago, Illinois, October 16, 1960. Dr. Harry L. Mueller of Boston, Massachusetts, Chairman of the Allergy Section presented Dr. Glaser with a scroll which read as follows:

> By unanimous vote of the Section on Allergy of the American Academy of Pediatrics assembled in Chicago, Illinois at the Twenty-ninth Annual Meeting of the Academy, this Scroll is awarded to
>
> Jerome Glaser, M.D.
>
> as an expression of gratitude and appreciation for his untiring services in advancing the study of pediatric allergy: for his brilliant teaching of pediatric allergy at the University of Rochester School of Medicine and Dentistry and in this Academy for many years: as originator of the plan which ultimately led to the formation of what is now the Allergy Foundation of America: as author of the first comprehensive text-book on allergy in childhood: as a pioneer investigator in advancing our knowledge of the prophylaxis of allergic disease.
>
> For the Section:
> Arthur J. Horesh, M.D.
> Harry L. Mueller, M.D., *Chairman*

# In Memoriam

### HENRY M. BLACKBURN, M.D.

Dr. Henry M. Blackburn of Grand Rapids, Michigan, graduated from the Vanderbilt University School of Medicine in 1913. He received specialized training at Rush Medical College of the University of Chicago. He was a member of the Kent County Medical Society, the Michigan State Medical Society, and the American Medical Association. Dr. Blackburn was a fellow of the American Society of Ophthalmologic and Otolaryngologic Allergists. He served on the staffs of Butterworth, Blodgett Memorial and St. Mary's Hospitals. During the Mexican border campaign, he was a captain attached to the 32nd division in the Army Medical Corps and during World War I, he served in France. Dr. Blackburn is survived by his wife, Louise.

Dr. Blackburn became a member of the College in 1945.

F. K. Hansel

# Papers of Interest

Garner, R. C.: Erythema multiforme associated with sulfamethoxypyridazine administration. New England J. Med., 261:1173 (Dec. 3), 1959.
Title compound, when administered in large doses, caused appearance of erythema multiforme in three children.

Wallace, I. R.: Sulphamethoxypyridazine in the treatment of respiratory infections in children. Practitioner, 184:613 (Nov.), 1959.
Title compound and sulfadimidine were compared. In 61 subjects one daily dose was sufficient, as effective, and less toxic.

Harkins, H. P.: Treatment of pharyngitis and laryngitis with an improved hydrogen peroxide. Eye, Ear, Nose & Throat Month., 38:942 (Nov.), 1959.
In 53 patients the itching sensation of burning and local discomfort of pharyngitis (in smokers) was relieved by topical application of urea peroxide (10 per cent) in glycerol.

U. S. Public Health Service TB therapy trial: Hepatic toxicity of pyrazinamide used with isoniazid in tuberculosis patients. Am. Rev. Respiratory Dis., 80:371 (Sept.), 1959.
Confirmation that pyrozinamine when used with isonicotinic acid hydrazide possesses specific hepato-toxic properties.

Brunelle, P.: The toxic effect of kanamycin on the inner ear: report of a case. Canad. M.A.J., 81:381 (Sept. 1), 1959.
Although kanamycin was life saving in an 18-year-old girl suffering from septicemia, permanent cochlear and vestibular damage occurred.

Anderson, P. C., and Wissinger, H. A.: Incidence of cutaneous eruption due to sulfamethoxypyridazine. U. S. Armed Forces M. J., 10:1051 (Sept.), 1959.
The incidence of reactions was 2.7 per cent of 223 patients. All recovered quickly.

Dittman, W. A., and Ward, J. R.: Demecolcine toxicity. A case report of severe hematopoietic toxicity and a review of the literature. Am. J. Med., 27:519 (Sept.), 1959.
Toxic effects, especially of the hematopoietic system, are reviewed.

Hallett, W. Y., Beall, G. N., and Kirby, W. M. M.: Chemoprophylaxis in chronic obstructive pulmonary emphysema. A twelve-week study with erythromycin. Am. Rev. Respiratory Dis., 80:716 (Nov.), 1959.
The patients to whom placebos were issued did as well as those treated with erythromycin.

Wilson, G. S.: Faults and fallacies in microbiology. J. Gen. Microbiol., 21:1 (Aug.), 1959.
Required reading!

Murdoch, J. M., Leckie, W. J. H., Downie, J., Swain, R. H. A., and Gould, J. C.: An evaluation of continuous antibiotic therapy in chronic bronchitis. Brit. Med. J., 2:1277 (Dec. 12), 1959.
When oxytetracycline is administered daily to patients with advanced bronchitis, exacerbations are safely, reliably, and inexpensively prevented.

Bukantz, S. C.: Principles of management with corticosteroid drugs. Illinois Med. J., 116:263 (Nov.), 1959.
In children in whom there is a tuberculin test, isonicotinic acid hydrozide and para-amino, salicylic acid, are administered during and for one month after cessation of, treatment with corticosteroid hormones.

Jasmin, G., and Bois, P.: Anti-inflammatory corticosteroids: their pharmacological evaluation. Internat. Rec. Med., 172:731 (Dec.), 1959.
Although anti-inflammatory and anti-anabolic effects of corticosteroid hormones are related, the latter can selectively be neutralized. There are other non-steroidal mediating effects of stress on inflammation.

Gomsa, J.: Influence of the thymus upon the egg-white allergy in the rat. Nature, 184:1726 (Nov. 28), 1959.
In thymectomized rats, the reaction to egg white is decreased in degree, and can be restored by antecedent injection of thymus extract. When adrenalectomized, the shock is severe, and independent of thymectomy or thymus extract injection.

Goth, A.: Inhibition of anaphylactoid edema in the rat by 2-deoxyglucose. Am. J. Physiol., 197:1056 (Nov.), 1959.
Intravenous injection of 2-deoxyglucose in doses of 200 mg/kg IV inhibits dextran or ovomucoid-induced anaphylactoid edema of rats.

Nossal, G. J. V.: Antibody production by single cells. III. The histology of antibody production. Brit. J. Exper. Pathol., 40:301 (Aug.), 1959.
Conclusions suggest that cells of plasma type may be the chief, if not the only, cells which produce antibody.

Lackenbacher, R. S.: Pruritic dermatoses. Med. Times, 87:1629 (Dec.), 1959.
In 76 patients afflicted with pruritic dermatoses, dexamethasone in diminishing doses adequately controlled itching and exudation.

Beer, D. T., and Schaffner, F.: Fatal jaundice after administration of beta-phenylisopropylhydrazine. J.A.M.A., 171:887 (Oct. 17), 1959.
Noted after administration of about 600 mg over a period of six weeks. The findings in the liver are similar to those caused by iproniazid and cannot be differentiated from severe viral hepatitis.

Christensen, C. N.: Reactions to poliomyelitis vaccine. J.A.M.A., 171:869 (Oct. 17), 1959.
Following injection of 184,000,000 doses of polio vaccine, 138 reported burning or stinging; 56 allergic; 37 neurological; 11 febrile, 17 local, and 25 unspecified and miscellaneous reactions.

Cronheim, G. E., and Toekes, I. M.: The effect of 2-dimethylaminoethanol (deanol) or anaphylactoid edema in rats. J. Pharmacol. & Exper. Ther., 127:167 (Oct.), 1959.
Title drug inhibits anaphylactoid edema resulting from subcutaneous injection into rats' paws of eggwhite, serotonin, formaldehyde or histamine.

Schmid, E., Zicha, L., Scheiffarth, F., and Buttner, O.: Antagonism of antihistaminic drugs against serotonin. Arzneimittel-Forsch., 9:474 (Aug.), 1959.
Using guinea pigs in whom asthma was induced by either histamine or serotonin, 11 antihistaminic agents acted also against serotonin in ratios of 1:15 to 1:60.

Shirinskaya, A. I.: The effect of penicillin on certain defence functions of the body. II. The effect of penicillin on the blood proteins and on the allergic reaction in experimental animals. Antibiotics (USSR), 4:55 (Jan.-Feb.), 1959.
One injection into mice of the tolerance dose of penicillin reduced the symptoms of anaphylactic shock.

Epp, M.: Serological procedure for the detection of antibodies to penicillin, Science, 130:1472 (Nov. 27), 1959.
Bis-diazotized benzidine couples erythrocytes to penicillin T. Their hemagglutination detects antibodies to penicillin in "allergic" subjects.

Grater, W. C.: Combined steroid-ataractic therapy in allergy. Internat. Rec. Med., 172:672 (Nov.), 1959.
Better results recorded in anxious, asthmatic patients and in those with allergic dermatitidies.

MacLaren, W. R.: Acute and chronic asthma. Treatment with theophylline in hydroalcoholic solution: clinical evaluation and pulmonary function studies. California Med., 91:278 (Nov.), 1959.
In sixty-one asthmatic patients, title preparation helped control bronchospasm.

Zelman, S.: Liver cell necrosis in chlorpromazine jaundice (allergic cholangiolitis). A serial study of twenty-six needle biopsy specimens in nine patients. Am. J. Med., 27:708 (Nov.), 1959.
No evidence of permanent sequelae, but resolution of portal infiltration may be associated with transient portal fibrosis.

Watson, J. F., and Katz, F. H.: Hypokalemic nephropathy in an adrenalectomized patient. Am. J. Med., 27:844 (Nov.), 1959.
Hypokalemia, polyuria, polydipsia and hyposthenuria were observed in an adrenalectomized patient to whom 9-alpha-fluorohydrocortisone was administered, probably in excess.

Doubrow, S., Roux, M., and Chatelin, C. L.: Problems of immunobiology in cancers. Allergic effects of devitalized antigenic implants. Presse med., 67:1867 (Oct. 28), 1959.
One field of the future.

Dubow, E.: Advantages of a new salicylate in immunization reactions in infants. Arch. Pediat., 76:455 (Nov.), 1959.
Pain or fever caused by immunization procedure was lessened in twenty infants to whom choline salicylate was administered.

Colldahl, H., Alvager, T., and Uhler, J.: A new method for studying the functioning of the lungs. Nature, 184:372 (Aug. 1), 1959.
Normally functioning lungs eliminate acetylene and argon at the same rate. In a patient with sarcoidosis, argon was eliminated more slowly.

Fogel, D.: Sjogren's syndrome with benign purpura hyperglobulinemia. New England J. Med., 261:31 (July 9), 1959.
Reported is the second case of purpura hyperglobulinemia with Sjogren's syndrome (kerato-conjunctivitis sicca).

Koch, D.: Diagnosis of capillary bronchiolitis. Am. J. Roentgenol., 82:433, 1959.
The earliest sign is concavity of posterior part of the diaphragm. The lung bulges anteriorly.

Doust, J.: Actions and significance of serotonin. Mod. Med., 27:25 (Nov. 15), 1959.
If you missed this, go back and find it. Worth keeping.

Sulzberger, M., and Kopf, A.: Treatment of atopic dermatitis. World Wide Abstracts, 2:11 (Dec.), 1959.
Feature article. Should be read by every physician who treats the title disorder.

Dorsey, C.: Algerian ivy dermatitis; A California disease. California Med., 90:155 (Feb.), 1959.
Twelve patients suffered from contact dermatitis within twenty-four to forty-eight hours after touching plants. All but one who needed corticotropin responded to oral corticosteroid hormones.

Baker, R.: Cultivation of the common cold virus. Brit. M. J., 5169:334 (Jan. 30), 1960.
Editorial review of present knowledge of title subject.

Morris, G.: The serendipity involved in finding the cause of shoe-leather dermatitis. Connecticut Med., 23:714 (Nov.), 1959.
An honest investigator's nine bits of serendipity and the subsequent twelve years' work it took to prove every one concerned was wrong.

Towner, C.: Familial incidence of the Henoch-Schönlein syndrome. Brit. M. J., 5163:1385 (Dec. 19), 1959.
Second reported case of familial incidence. One sibling reacted after immunization for diphtheria, and the second, following an upper respiratory infection.

# Books of Interest

HYPNOSIS IN SKIN AND ALLERGIC DISEASES. By Michael J. Scott, M.D. 161 pages. Springfield, Illinois: Charles C Thomas, 1960. Price, $6.50.

Hypnotherapy is an effective multifunctional technique permitting directness and acceleration in psychotherapy. In certain judiciously selected dermatologic and allergic cases, no other form of therapy can produce such rapid and beneficial results. Whether psychotherapy is utilized merely for supportive therapy or symptom removal, or toward uncovering subconscious motivations and conflicts as etiologic factors, hypnosis will prove invaluable in enabling the physician to secure rapid and effective results.

The concept of psychosomatic pertains to the interaction of emotions and bodily functions in the production of symptoms. Certain cutaneous and allergic diseases should be objectively observed and treated as dynamic, constantly fluctuating adaptations to the stresses and strains to which the patient is exposed both externally and internally.

There is a definite trend in dermatology and allergy to the psychosomatic approach in treatment when indicated. The introduction of psychiatric thinking into dermatologic and allergic disorders enables a physician to attain therapeutic results far beyond those expected from organic therapy alone.

Theoretically, some use of psychotherapy could be made in any skin or allergic condition which has an emotional component involved. This holds true whether the emotional disturbance is a factor in the production of the illness or is merely the result of organic distress.

Skillfully applied psychotherapy can accomplish much for the sick patient when practiced in conjunction with appropriate conventional medical therapy. By those trained in hypnosis, much may be accomplished in many cutaneous and allergic diseases. Best results with hypnotherapy can be anticipated in cases where the cause is primarily emotional and less where organic components predominate.

One method of reconditioning or re-educating the subconscious through hypnosis is by replacing one habit pattern with another, more constructive pattern. In symptom substitution, some undesirable mental or physical outlet is replaced by a more acceptable one. Scratching, for example, may be replaced by a desire to do physical exercise.

In private practice, patients with primarily somatic disease seldom are therapeutic problems in comparison to those with primarily psychosomatic or functional complaints. In the latter group, difficulty is frequently encountered in securing satisfactory response to conventional medical therapy alone. In such instances combined dermatologic, allergic and hypnotherapy is frequently the treatment of choice.

*From the Author's Introduction*

OCCUPATIONAL DISEASES AND INDUSTRIAL MEDICINE. By Rutherford T. Johnstone, M.D., and Seward E. Miller, M.D. 482 pages. W. B. Saunders Co., 1960. Price $12.

It is not presumptuous to preface this book with the declaration that it has been written in response to demand. With the continued decentralization and expansion of industry, the practitioners of general medicine throughout the land now are caring for the majority of industrial workers. Then, too, on the farm and in the home a great variety of chemicals, from detergents and metal polishes to pesticides, are in

everyday use. With this increased exposure of the public to toxic materials, almost all physicians are confronted with situations once more closely confined to the practice of industrial medicine. Moreover, establishment of the new specialty of occupational medicine, with initiation of residency training, has created a demand by students and their teachers for a textbook fulfilling their needs. For these practitioners, students and teachers, more than for the experts in the field, this book has been written.

Part I covers the broad spectrum of industrial medicine. Here will be found information about the multiple facets of medical practice as they relate to industry and to our industrial society, culminating in Chapter 7, The Diagnosis of Occupational Disease. Part II is devoted to the clinical approach to occupational diseases and largely retains the format used in earlier books written by the senior author. His clinical and toxicologic experience combined with the clinical teaching and pathologic experience of the junior author, provides a more complete coverage of the occupational disease entities than otherwise could be accomplished.

Part I and Part II are preceded by introductions designed particularly for the indoctrination of newcomers to this field. The introduction to Part I portrays the opportunities, needs and characteristics of the practice of industrial medicine. In the succeeding chapters are portrayed the scope and elements of industrial medicine, the duties of occupational health personnel, industrial medicine and insurance, and man's adaptation to industrial life.

The introduction to Part II serves as a basis for a better understanding of the occupational diseases. Of particular importance is the description of the manner in which inhaled gases accumulate in body tissues and how they are eliminated. In addition, some pertinent chemistry and toxicology are reviewed as a prelude to the technical material that follows. Attention is invited to the scope and clinical approach of the material on occupational diseases; not only chemical intoxication, but occupational infections, cancer and diseases from exposure to physical forces in the work environment are portrayed. Under prevention, industrial hygiene principles have been incorporated. This material is enhanced by numerous illustrations.

Frequently the worker-patient will refer to a certain industrial process or to materials and in so doing uses a terminology foreign to his physician. To aid the physician in this regard, an extended glossary of the more common terms used in industry has been appended.

*From the Authors' Preface*

---

"We ought then," Laplace wrote, "to regard the present state of the universe as the effect of its anterior state and as the cause of the one which is to follow. Given for one instant an intelligence which could comprehend all the forces by which nature is animated and the respective situation of the beings who compose it—an intelligence sufficiently vast to submit these data to analysis—it would embrace in the same formula the movements of the greatest bodies of the universe and those of the lightest atom; for it, nothing would be uncertain and the future, as the past, would be present to its eyes."